

FOOD AND DRUG ADMINISTRATION

Center for Drug Evaluation and Research

Meeting of the Anesthetic and Life Support Drugs Advisory Committee

Bethesda Marriott Hotel, 5151 Pooks Hill Road, Bethesda, MD

August 19, 2010

Background Package

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FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA AND ANALGESIA PRODUCTS

MEMORANDUM

DATE: July 26, 2010

FROM: Bob A. Rappaport, MD
Director
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II, CDER, FDA

TO: Chair, Members and Invited Guests
Anesthetic and Life Support Drugs Advisory Committee (ALSDAC)

RE: Overview of the August 19, 2010, ALSDAC Meeting to Discuss
NDA 22-516 for Cymbalta for the Treatment of Chronic Pain

At this meeting of the ALSDAC, we will be discussing the New Drug Application for Cymbalta (duloxetine) for the treatment of chronic pain, submitted by Eli Lilly and Company. Cymbalta is a selective serotonin and norepinephrine reuptake inhibitor initially approved in 2004 for the treatment of major depressive disorder, and subsequently approved for the indications of pain associated with diabetic peripheral neuropathy (DPN) in 2004, generalized anxiety disorder and maintenance treatment of major depression in 2007, and fibromyalgia in 2008. The exact mechanisms of the antidepressant, central pain inhibitory and anxiolytic actions of duloxetine in humans are unknown, however they are believed to be related to its potentiation of serotonergic and noradrenergic activity in the central nervous system. If approved, Cymbalta will be the first non-traditional analgesic, e.g., non-NSAID, non-opioid analgesic, broadly indicated for the treatment of chronic pain.

The safety profile for Cymbalta as reflected in the product label includes the antidepressant drug class boxed warning for suicidality in children, adolescents, and young adults taking antidepressants for major depressive disorder and other psychiatric disorders. Other serious adverse events associated with Cymbalta and noted in the label include hepatotoxicity, orthostatic hypotension and syncope, serotonin syndrome, seizures, bleeding and effects on blood pressure. During the meeting, the safety of Cymbalta will be discussed in detail, including an in depth discussion of the

hepatotoxicity associated with the product and a summary of the available postmarketing data.

The Applicant has submitted efficacy studies conducted in patients with chronic pain due to diagnosed osteoarthritis and low back pain. The results of these studies will be presented during the meeting and, in addition to the previous demonstration of Cymbalta's efficacy for the treatment of DPN and fibromyalgia, would constitute the basis for the chronic pain indication. For the indication of the treatment of chronic pain, the Division believes that efficacy should be demonstrated in a variety of chronic pain conditions. Particularly for a drug that is not a "traditional analgesic," and where the mechanism of action is not well defined, the weight of evidence for a chronic pain indication may be greater than for analgesics such as opioids and NSAIDs. We have determined that the particular mix and number of patient populations studied in the Cymbalta development program would be adequate to support this broadened indication.

At this meeting of the ALSDAC, you will be asked to discuss the following issues related to the Cymbalta application:

- Whether the clinical trials in chronic low back pain and osteoarthritis provide adequate evidence of the efficacy of Cymbalta for the treatment of chronic pain in those conditions
- Whether there is evidence that exposure to Cymbalta results in clinically concerning hepatic toxicity
- And, if this evidence of hepatotoxicity does exist, what are the implications for the overall risk-benefit balance for Cymbalta for the treatment of chronic pain

During these discussions, we ask that you keep in mind that the approval of Cymbalta for the treatment of chronic pain will likely result in a substantial increase in the prescribing of the product in the general population given the large number of Americans suffering from these types of chronic pain conditions. Thank you in advance for participating in this meeting and providing us with your expertise and insights on this important public health issue.

Summary of NDA 22-516

Cymbalta for Treatment of Chronic Pain

Cymbalta (duloxetine) is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) approved initially in August, 2004, as an anti-depressant, and subsequently for indications of the pain associated with diabetic peripheral neuropathy (DPN) in 2004, generalized anxiety disorder (GAD) and maintenance treatment of major depression (MDD) in 2007, and fibromyalgia (FM) in 2008. This New Drug Application (NDA 22-516) is in support of a supplemental indication for the treatment of chronic pain.

A chronic pain application for duloxetine (NDA 22-333) was previously submitted by Eli Lilly on May 15, 2008 and subsequently withdrawn on November 26, 2008, after the Applicant was notified that the Division did not agree with the efficacy results in the submission. At the time there was an additional ongoing study in OA for which results were not yet available.

The mechanism of action of duloxetine (DLX) in the treatment of chronic pain is different from that of drugs already approved for this indication, such as opioids and nonsteroidal anti-inflammatory drugs (NSAIDs). Serotonin and norepinephrine are thought to mediate analgesic mechanisms in the brain and spinal cord. Duloxetine is believed to act via the potentiation of descending inhibitory pain pathways.

To support a chronic pain indication, the Applicant has conducted clinical trials in four chronic pain conditions: DPN, FM, pain associated with osteoarthritis (OA), and chronic low back pain (CLBP). In addition to the already approved pain indications of DPN (NDA 21-733) and fibromyalgia (NDA 22-148), the Applicant has submitted the following five new clinical trials, three in CLBP, and two in OA: HMEP (OA trial), HMFG (OA trial), HMEN (CLBP trial), HMEO (CLBP trial), and HMGC (CLBP trial). Three of the trials (HMEO, HMEN, and HMEP) were also included in NDA 22-333.

Overview of OA and CLBP Clinical Trials

All five OA and CLBP trials were considered adequate and well-controlled based on the trial design. All were multicenter, randomized, double-blind, placebo-controlled trials with a duration of the double-blind treatment of at least 12 weeks. The design of each trial is summarized in the table that follows.

Trial/ Number of randomized patients (N)	Design	Treatments	Duration	Primary Endpoint(s)
HMFG (OA) N=128 DLX N=128 placebo	Double-blind (DB), placebo-controlled (PC), parallel-group, flexible dose Objective: Efficacy of combined 60 to 120 mg DLX	<u>Initial Randomization:</u> <ul style="list-style-type: none"> Placebo and DLX 60 mg/day <u>At Week 7 non-responders re-randomized to DLX:</u> <ul style="list-style-type: none"> Titrated up to 120 mg/day 	13 weeks	Reduction in 24h average pain item of the Brief Pain Inventory (BPI)
HMEP (OA) N=111 DLX N=120 placebo	DB, PC, parallel-group <u>Objective:</u> Efficacy of combined 60 to 120 mg DLX	<u>Initial Randomization:</u> <ul style="list-style-type: none"> Placebo and DLX 60mg/day <u>At Week 7 all patients receiving DLX re- randomized to:</u> <ul style="list-style-type: none"> 60mg/day 120mg/day 	13 weeks	Reduction in weekly mean of 24h average pain ratings from patient diaries
HMEN (CLBP) N=115 DLX N=121 placebo	DB, PC, parallel-group <u>Objective:</u> Efficacy of combined 60-120 mg DLX	<u>Initial Randomization:</u> <ul style="list-style-type: none"> Placebo and DLX 60 mg/day <u>At Week 7 non-responders re-randomized to DLX:</u> <ul style="list-style-type: none"> Titrated up to 120 mg/day 	13 weeks	Reduction in 24h average pain item of the BPI
HMEO (CLBP) DLX N=59 20 mg/day N=116 60 mg/day N=112 120 mg/day N=117 placebo	DB, PC, parallel-group, fixed-dose <u>Objective:</u> Efficacy of DLX 60 mg	<ul style="list-style-type: none"> Placebo DLX 20mg/d DLX 60mg/d DLX 120mg/d 	13 weeks	Reduction in weekly mean of 24h average pain ratings from patient diaries
HMGC (CLBP) N=198 DLX N=203 placebo	DB, PC, parallel-group, fixed-dose <u>Objective:</u> Efficacy of DLX 60 mg	Placebo DLX 60 mg/day	12 weeks	Reduction in 24h average pain item of the BPI

All of the five primary chronic pain trials in OA and CLBP had similar key characteristics. Study subjects were required to have had chronic pain for at least three months prior to entry and a baseline pain score of four or greater on an 11-point Likert scale. Patients with MDD were excluded from all five trials. To focus on patients with non-neuropathic back pain, CLBP trials excluded patients with neurological deficits or clinical evidence of either central findings (spinal stenosis) or peripheral neuropathy (radiculopathy). Patients were allowed to remain on their regular dose of NSAIDs, provided that they were using them at the time of enrollment. Randomization was stratified by NSAID use.

The primary efficacy endpoint chosen by the Applicant for all OA and CLBP trials was the change from baseline to Week 13 (Week 12 for HMGC) in pain intensity. Pain intensity was measured by the BPI 24-hour average pain item on an 11-point Likert scale and was expressed as either a weekly mean from patient diaries (HMEP and HMEO) or as a single day report (HMEN, HMFG, and HMGC). The primary analyses were conducted on the modified intent-to-treat (mITT) population defined as all patients who were randomized and had baseline scores and at least one post-baseline observation. For the flexible-dose trials (HMFG, HMEP, and HMEN), the primary analyses were based on the combined 60/120 mg QD duloxetine arm versus placebo. In all five trials, a mixed-models repeated measures analysis (MMRM) was pre-specified for the primary efficacy measure. In addition, an analysis of covariance (ANCOVA) was used to compare treatments. The ANCOVA analysis was conducted using last observation carried forward (LOCF), baseline observation carried forward (BOCF), and modified BOCF (mBOCF) imputation strategies. In the mBOCF approach, a BOCF strategy was used to impute missing data from dropouts due to lack of efficacy (LOE) or adverse event (AE), and an LOCF strategy was used to impute missing data from dropouts due to other reasons. The MMRM, ANCOVA/LOCF and ANCOVA/BOCF analyses were also applied to the secondary measures. Secondary outcome measures were tested sequentially and included Patient's Global Impression of Improvement (PGI-Improvement) and disease-specific physical function scales including WOMAC physical function subscale for OA pain and RMDQ-24 for CLBP.

Efficacy Findings

Based on the pre-specified MMRM analysis, the Applicant found that duloxetine demonstrated a greater reduction in 24-hour average pain compared with placebo in three flexible-dose trials (HMEN, HMEP, and HMFG) for the combined 60 mg to 120 mg dose, and in one fixed-dose trial (HMGC) for the 60 mg dose. Results from the Applicant's ANCOVA/BOCF sensitivity analysis of the primary outcome measure confirmed positive results in three trials, HMEN, HMFG, and HMGC.

When the Division evaluated the Applicant's efficacy analyses and findings, several key points were identified as problematic. The MMRM analysis method was found not appropriate for a chronic pain trial because it assumes that dropouts occur at random, and utilizes data from patients who withdrew early from the trial, potentially assigning good pain scores to subjects who could not tolerate the drug, i.e., withdrew due to adverse events. In analgesic trials, early discontinuations should be considered treatment failures,

therefore an improvement in a subject's pain score prior to dropping out due to an adverse event should not be credited in the analysis. Analysis methods that impute missing data conservatively, such as BOCF, are preferred for these types of trials.

The statistical reviewer for this application reanalyzed the efficacy data for the pivotal trials using conservative imputation strategies. There was some concern that the mBOCF method potentially assigned good scores to patients that dropped out for reasons other than lack of efficacy or adverse events. The assignment of good scores in this scenario was concerning since reasons for dropouts reported as "other" and "subject decision" may have masked adverse events. Thus, primary focus was on the BOCF methodology. In addition, the Division conducted the analyses using the ITT population which consisted of all patients who were randomized and had baseline scores, regardless of whether they had a post-baseline observation, in contrast to the method used by the Applicant.

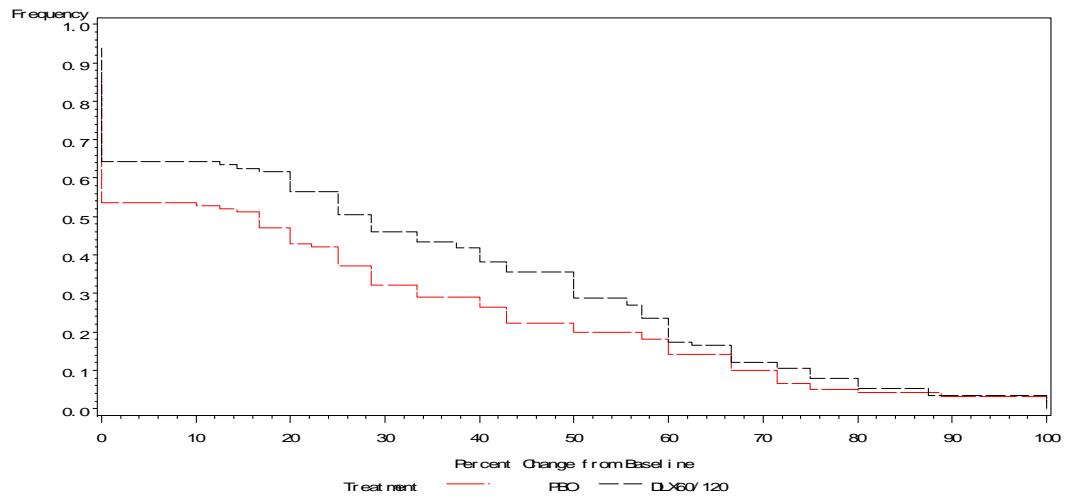
Based on the Division's analyses, the combined 60 mg to 120 mg duloxetine dose was found superior to placebo for reducing pain intensity at Week 13 in one OA trial (HMFG) and one CLBP trial (HMEN). In analyses of the duloxetine 60 mg dose only, superiority of duloxetine to placebo for reducing pain intensity was demonstrated at Week 12 in one CLBP, fixed-dose trial (HMGC) and in two, one OA and one CLBP, flexible-dose trials (HMEN and HMFG), at Week 7 as well as at Week 13.

The table that follows summarizes the collective evidence from the Applicant's primary and sensitivity analyses, as well as the Division's additional analyses, of both the combined 60 to 120mg duloxetine treatment, and of 60 mg duloxetine alone.

Prespecified Primary Analysis of 60mg-120mg	HMEN (CLBP)		HMEP (OA)	HMFG (OA)		HMGC (CLBP)
MMRM	P<0.05		P<0.05	P<0.05		
ANCOVA/BOCF	P<0.05		NS	P<0.05		
DLX60mg	Week 13	Week 7		Week 13	Week 7	Week 12
MMRM	P<0.05		NS			P<0.05
ANCOVA/BOCF	P<0.05	P<0.05	NS	P<0.05	P<0.05	P<0.05

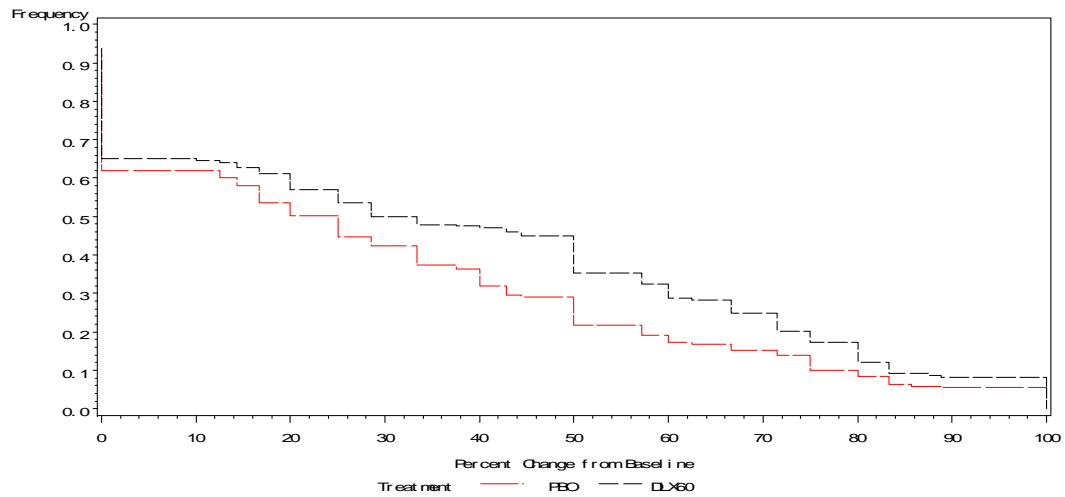
Exploratory continuous responder curves were generated for the Phase 3 trials. The graphs depict the cumulative proportion of responders across all possible levels of response. Statistically significant separation between placebo and DLX was demonstrated in Trials HMEN, HMGC, and HMFG.

Continuous responder analysis - HMEN



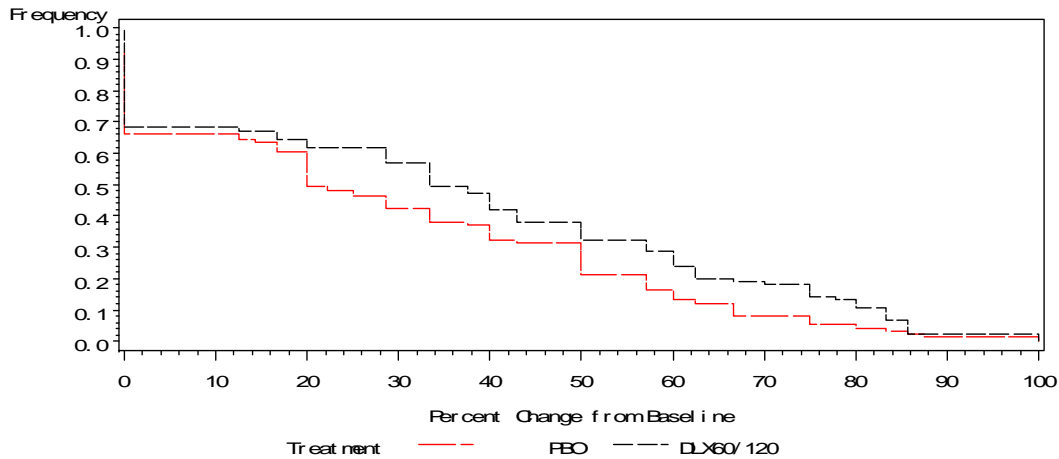
P-value of 0.018 generated by van der Waerden test.

Continuous responder analysis – HMGC



P-value of 0.024 is generated by van der Waerden test.

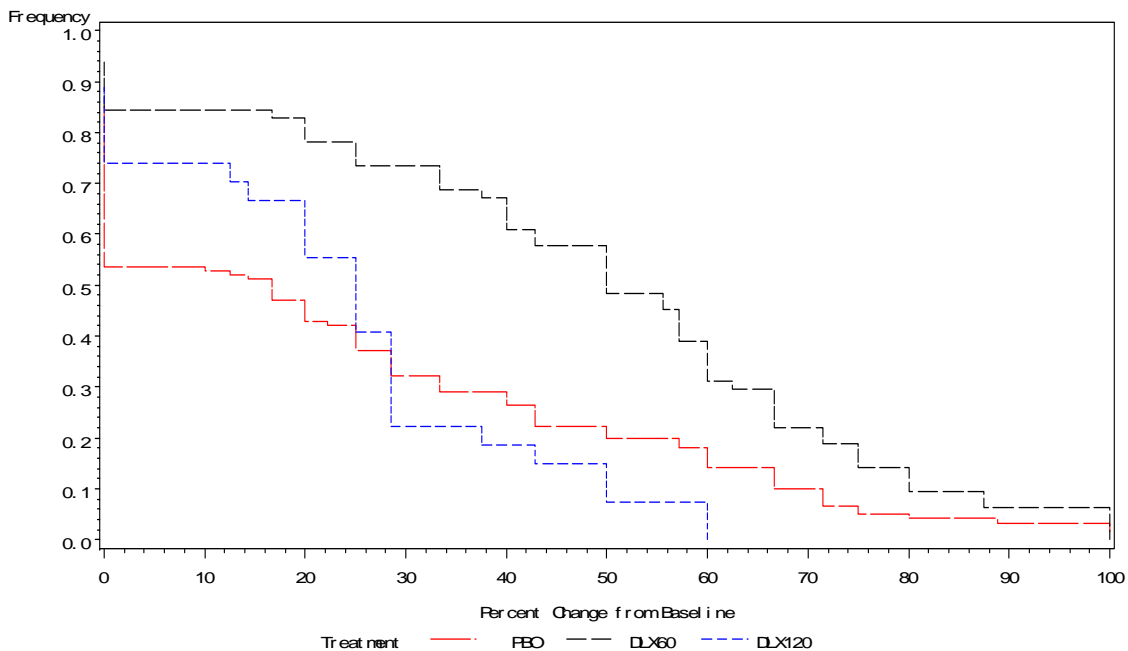
Continuous responder analysis – HMFG



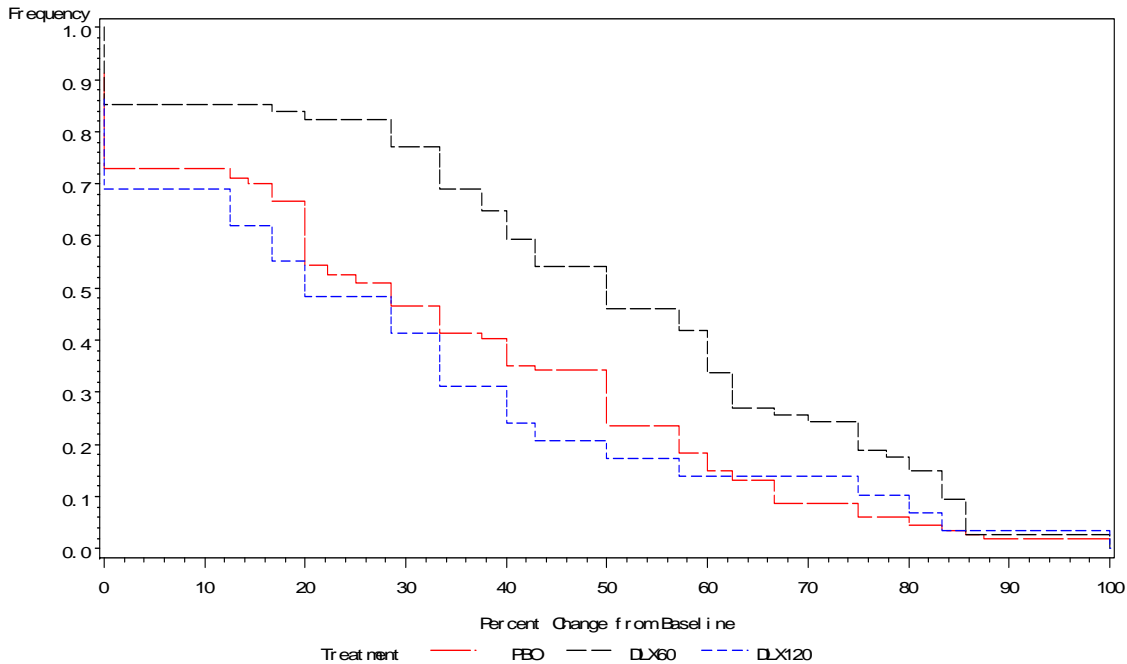
P-value of 0.016 is generated by van der Waerden test.

To elucidate the effect of the 120 mg dose (60 mg for seven weeks followed by 120 mg for six weeks) in two trials HMEN and HMFG, exploratory responder curves were generated. The graphs suggest that the duloxetine 120 mg dose group may not have contributed to the efficacy of the drug.

Exploratory continuous responder curves – HMEN



Exploratory continuous responder curves – HMFG



Summary of Efficacy Findings

1. In terms of the primary efficacy endpoint analyses based on the Division's preferred conservative method of imputation, the following trials provide evidence for efficacy of duloxetine as a treatment for chronic pain in patients with osteoarthritis and chronic low back pain
 - a. Trial HMEN demonstrated efficacy of duloxetine 60-120mg in the treatment of chronic low back pain.
 - b. Trial HMGC demonstrated efficacy of duloxetine 60mg in the treatment of chronic low back pain.
 - c. Trial HMFG demonstrated efficacy of duloxetine 60-120mg in the treatment of chronic pain associated with osteoarthritis.
2. The separation of the continuous responder curves further support the efficacy of duloxetine 60-120 mg.
3. Additional *post hoc* analyses demonstrated:
 - a. Trials HMFG (OA) and HMEN (CLBP) demonstrated efficacy of duloxetine 60mg at Week 7 (of 13 week trial).
 - b. There is no evidence, according to an exploratory analysis, that duloxetine 120mg confers benefit over duloxetine 60mg for patients who did not respond to 60mg during the first 7 weeks of treatment.

Safety Findings

Review of safety data from OA and CLBP trials did not identify any new or unexpected safety signals. The overall safety profile in OA and CLBP patients resembled the established safety profile for the duloxetine described in the current product label. No deaths were reported during any of the trials. Duloxetine-treated patients presented with a higher incidence of serious adverse events (SAEs) compared to placebo-treated patients. While there was an overall treatment group difference in the incidence of SAEs, no significant difference between treatment groups was observed for individual SAEs. Significantly more duloxetine-treated patients discontinued due to adverse events compared with placebo-treated patients. The most common reasons for early discontinuation were gastrointestinal (nausea) and sleep disturbance (somnolence/insomnia) related symptoms. Significantly more duloxetine-treated patients compared to placebo-treated patients experienced at least one treatment-emergent adverse event (TEAE). Patients in the OA and CLBP trials experienced the following common adverse events more frequently with duloxetine than placebo treatment: nausea, insomnia, dizziness, dry mouth, somnolence, constipation, and fatigue. Most of these events were dose dependant.

Analyses of hepatic laboratory analytes and hepatic-related AEs from OA and CLBP trials did not identify safety information that differs from what has been seen in placebo-controlled trials with duloxetine for the other approved indications. The most commonly reported hepatic-related treatment-emergent adverse event (TEAE) was hepatic enzyme increase. Elevation in AST/ALT was not associated with bilirubin elevation. No patients met the Hy's Rule criteria. Increase in transaminases was more frequently reported with duloxetine 120 mg dose compared to duloxetine 60 mg dose. However, no difference in the magnitude of the transaminase elevations was observed between the 60 mg and the 120 mg duloxetine dose groups. Analysis of the cases with elevated liver enzymes over time showed that the majority returned to baseline after drug discontinuation, and for some cases with less than three times the upper limit of normal increase, enzyme levels returned to baseline with continued treatment with duloxetine. The majority of the reported hepatic-related TEAEs occurred in patients with pre-existing liver enzyme abnormalities. Markedly abnormal increases in ALT and AST were infrequent in the primary chronic pain trials. Because of the small numbers it was difficult to evaluate for dose response. When such elevations occurred, ALT and AST levels either normalized or were trending back towards normal values at subsequent visits.

Background Document

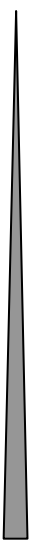
Cymbalta Advisory Committee Meeting

Chronic Pain Indication: History and Current Regulatory Requirements for Approval

Over the years, FDA has approved analgesics for a wide range of indications, from very narrow indications such as “management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain” to very broad indications such as “management of pain.”

Indications that allow for on-label use for the treatment of chronic pain include indications for drugs that contain a specific statement for treatment of chronic pain, those that do not exclude chronic pain (i.e., moderate-to-severe pain), or those that specify a particular type of chronic pain, i.e., painful diabetic peripheral neuropathy (DPN) or fibromyalgia.

The following table shows examples of indications that have been granted for analgesics ranging from narrow to broad in scope.

	Indication	Drugs
N A R R O W 	Management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain	Oral transmucosal fentanyl citrate, fentanyl buccal soluble film, fentanyl buccal tablet
	Treatment of acute painful shoulder	Indomethacin, Sulindac
	Management of neuropathic pain associated with diabetic peripheral neuropathy	Duloxetine, Pregabalin
	Management of post-herpetic neuralgia in adults	Gabapentin
	Treatment of fibromyalgia	Pregabalin, Duloxetine, Milnacipran
	Short-term (≤ 5 days) management of moderately severe acute pain that requires analgesia at the opioid level, usually in a postoperative	Ketorolac
	Treatment of moderate-to-severe pain not responsive to non-narcotic analgesics.	Methadone

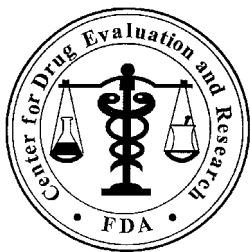
	Relief of moderate-to-severe acute and chronic pain where use of an opioid analgesic is appropriate.	Morphine oral solution
	Management of persistent, moderate to severe chronic pain that requires continuous, around-the-clock opioid administration for an extended period of time, and cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids	Fentanyl transdermal system
	Management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time.	Tramadol ER
	Management of moderate-to-severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time	Extended release formulations of morphine, oxycodone, oxymorphone, and hydromorphone
	Relief/management of moderate-to-severe acute pain where the use of an opioid is appropriate	Immediate release formulations of oxycodone and oxymorphone
	Management of pain where use of an opioid analgesic is appropriate	Immediate release hydromorphone, butorphanol tartrate nasal spray
	Relief of mild-to-moderate pain	Diflunisal, Diclofenac, Ibuprofen, Propoxyphene
B R O A D	Relief of moderate-to-moderately severe pain	Tramadol IR
	Relief of moderate-to-severe pain	Meperidine, Pentazocine
	Management of acute pain in adults	Celecoxib
	Management of pain	Naproxen, Etodolac

Of course, the treatment of chronic pain often includes the use of off-label drugs, either a drug not approved to treat pain at all, or a drug approved for a type of pain other than the one being treated. These include antidepressants (tricyclics, SNRIs), anticonvulsants, corticosteroids, antiarrhythmics and muscle relaxants. These drugs may or may not have

been shown to be effective via randomized controlled clinical trials in the conditions in which they are used.

The Agency is working to balance the need for adequate scientific rigor for demonstration of efficacy for the treatment of chronic pain with the feasibility of studying every patient population in which chronic pain occurs. At this time, to obtain a claim for the treatment of chronic pain, we recommend that sponsors study as wide a variety of conditions as possible, and demonstrate the efficacy of their product in neuropathic pain conditions, both central and peripheral, and non-neuropathic pain conditions. We are informing sponsors they should have replicated studies demonstrating efficacy in at least one indication from each category of chronic pain, including peripheral neuropathic pain (i.e., diabetic peripheral neuropathy, post-herpetic neuralgia, chemotherapy induced neuropathy), central neuropathic pain (stroke syndrome, spinal cord injury), and non-neuropathic pain (i.e., osteoarthritis, low back pain). In addition, there should be at least one positive trial in an additional one or two conditions in each major category of chronic pain. At present, if a Sponsor can submit a collection of studies that meets a “weight-of-evidence” argument; we would consider granting a general chronic pain indication, although we intend to include negative studies in the labeling and the relevant types of pain that were not studied.

For drugs that are not “traditional analgesics,” such as duloxetine, where the mechanism of action for analgesia is not well defined, or for new molecular entities without any historic use in the treatment of pain, the weight of evidence required for a chronic or general pain indication may be greater than for drugs such as opioids and NSAIDs, where the mechanisms of action are well defined and there is extensive use of these drugs for a multitude of painful conditions.



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: July 12, 2010

To: Ellen Fields, MD
Medical Officer
Division of Anesthesia, and Analgesia Products (DAAP)
Office of New Drugs

Through: Laura Governale, PharmD, MBA
Drug Use Data Analyst Team Leader
Division of Epidemiology
Office of Surveillance and Epidemiology

From: Rajdeep Gill, PharmD
Drug Use Data Analyst
Division of Epidemiology
Office of Surveillance and Epidemiology

Subject: Cymbalta® (duloxetine HCl) Drug Utilization Review

Drug Name(s): Cymbalta® (duloxetine HCl)

Application Type/Number: NDA 22-516

Applicant/sponsor: Eli Lilly and Company

OSE RCM #: 2010-1208

EXECUTIVE SUMMARY

Division of Anesthesia and Analgesia Products (DAAP) requested drug utilization data for Cymbalta® (duloxetine HCl) in support of the Anesthetic and Life Support Drugs Advisory Committee to be held on August 19, 2010. The focus of this meeting is to discuss the risk and benefits of approving Cymbalta® (duloxetine HCl) for treatment of chronic pain. This analysis provides the utilization trends for Cymbalta® (duloxetine HCl) from drug approval in August 2004 through year 2009.

- Total dispensed prescriptions of Cymbalta® (duloxetine HCl) increased from approximately 5 million prescriptions in year 2005 to approximately 14.6 million prescriptions in year 2009 accounting for approximately 3-fold increase
- Cymbalta® (duloxetine HCl) 60 mg was the most commonly dispensed strength accounting for approximately 65% of total Cymbalta® (duloxetine HCl) dispensed prescriptions
- Approximately 80% of total dispensed Cymbalta® (duloxetine HCl) prescriptions were in patient age group 25-64 years old
- Approximately three-quarters of total dispensed prescriptions of Cymbalta® (duloxetine HCl) were dispensed to female patients
- Total number of unique patients receiving prescription of Cymbalta® (duloxetine HCl) in outpatient retail pharmacies increased from approximately 1.4 million patients in year 2005 to 2.8 million patients in year 2009 accounting for approximately 2 fold increase
- “General Practice/Family Medicine/Doctor of Osteopathy” was the top prescribing specialty group for Cymbalta® (duloxetine HCl) followed by “Psychiatry” and “Internal Medicine”
- Approximately one third of the diagnosis codes recorded that were associated with Cymbalta® (duloxetine HCl) use were for labeled indications such as “Major Depressive Disorder”(ICD-9 296.2 and 296.3), “Generalized Anxiety Disorder” (ICD-9 300-.2), “Fibromyalgia” (ICD-9 729.1) and “Diabetic Peripheral Neuropathy” (ICD-9 250.6 and 357.2)
- “Depressive Disorder, not elsewhere specified” (ICD-9 311.0) was the most common diagnosis code recorded (29.2%) that was associated with Cymbalta® (duloxetine HCl) use
- Approximately 7% of the diagnosis codes recorded were associated with “diseases of musculoskeletal system and connective tissue” (ICD-9 codes 710-739) which include chronic pain conditions such as arthritis and back pain
- Approximately 6.5% of the diagnosis codes recorded were associated with “headaches and nerve pain” (ICD-9 codes 337-359) which include “Chronic Pain Syndrome” (ICD-9 338.4) and “Chronic Pain, NOS” (ICD-9 338.2)

1 INTRODUCTION

The Division of Anesthesia and Analgesia Products is conducting an Advisory Committee Meeting on August 19, 2010 to discuss the risks and benefits of approving Cymbalta® (duloxetine HCl) for indication of chronic pain treatment, NDA 22-516. In support of the review of this new drug application, the Division of Epidemiology has been requested to provide drug utilization patterns of Cymbalta®

(duloxetine HCl). Using the currently available proprietary drug use databases licensed by the Agency, this review provides overall sales data, use by indication, and prescriber specialty from drug approval in August 2004 through year 2009.

2 BACKGROUND

Cymbalta® (duloxetine HCl) is a serotonin and norepinephrine reuptake inhibitor (SNRI) and is indicated for Major Depressive Disorder (MDD), Generalized Anxiety Disorder (GAD), Diabetic Pheripheral Neuropathy (DPN), and Fibromyalgia (FM) in adults.¹ The Agency is currently reviewing a new drug application (NDA), 22-516 for Cymbalta® (duloxetine HCl) for treatment of chronic pain. On August 19, 2010 an advisory committee meeting will be convened before the members of the Anesthetic and Life Support Drug Committee and will discuss the available safety and efficacy data for Cymbalta® (duloxetine HCl) as they relate to the proposed indication of treatment of chronic pain. To understand the utilization patterns, assess labeled and off labeled indications, and assess number of prescriptions stratified by prescriber specialty for Cymbalta® (duloxetine HCl), this drug utilization review provides the outpatient trends from drug approval in August 2004 through year 2009.

3 METHODS AND MATERIAL

3.1 DETERMINING SETTINGS OF CARE

IMS Health, IMS National Sales Perspectives™ data (*see Appendix 2 for detailed database descriptions*) were used to determine the setting in which Cymbalta® (duloxetine HCl) was sold. Sales of Cymbalta® (duloxetine HCl) by number of individual packages (Eaches) sold from the manufacturer into the various retail and non-retail channels of distribution were analyzed for the year of 2009 (*data not provided*). Retail pharmacy settings (chain stores, independent pharmacies, and food stores) accounted for approximately 76% of Cymbalta® sales.² Since the majority of the Cymbalta® (duloxetine HCl) market share was sold to U.S. outpatient retail settings, this review focused on the outpatient retail pharmacy utilizations, excluding mail order channels.

3.2 DATA SOURCES

Proprietary drug use databases licensed by the Agency were used to conduct this analysis. Outpatient drug utilization was measured from SDI, Vector One®: National (VONA). From these data sources, the estimates of the total annual number of prescriptions dispensed were obtained for Cymbalta® (duloxetine HCl) from year 2004 through year 2009. We also obtained the number of dispensed prescriptions stratified by the prescribing specialties for an aggregate time period from approval in August 2004 through April 2010. In addition, the number of patients receiving a dispensed prescription for Cymbalta® (duloxetine HCl) in the outpatient setting was obtained from the SDI, Total Patient Tracker database for year 2004 through year 2009. Diagnoses associated with the use of Cymbalta® (duloxetine HCl) were obtained from the SDI, Physician Drug and Diagnosis Audit™ for an aggregate time period from August 2004 through April 2010 (*see Appendix 2 for detailed database descriptions*).

¹ Cymbalta® (duloxetine) label-http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/0221481b1.pdf

² IMS Health, IMS Nationals Sales Perspectives™, Data extracted 6/10. Source File: 1006cymb.DVR

4 RESULTS

4.1 OUTPATIENT DISPENSED PRESCRIPTIONS FOR CYMBALTA® (DULOXETINE)

Table 1 in *Appendix 1* displays the total number of projected dispensed prescriptions of Cymbalta® (duloxetine HCl) in outpatient retail pharmacies for years 2004 to 2009. Cymbalta® (duloxetine HCl) prescriptions increased from approximately 5 million prescriptions in year 2005 to approximately 14.6 million prescriptions in year 2009 in U.S. outpatient retail pharmacies. Cymbalta® (duloxetine) 60mg was the most commonly dispensed strength followed by 30mg and 20mg in year 2004 through year 2009.

4.2 OUTPATIENT DISPENSED PRESCRIPTIONS FOR CYMBALTA® (DULOXETINE) STRATIFIED BY AGE

Table 2 in *Appendix 1* displays the total number of projected dispensed prescriptions of Cymbalta® (duloxetine HCl) by age (0-17, 18-24, 25-64, 65+ years) in U.S. outpatient retail pharmacies in year 2004 through year 2009.

The data stratified by age indicate that approximately 78% of total Cymbalta® (duloxetine HCl) prescriptions were dispensed to patient age group 25-64 years of age in year 2009. Although total number of prescriptions increased from 3.9 million to 11.4 million (approximately 3 fold increase) from year 2005 through year 2009, the percent share of total Cymbalta® (duloxetine HCl) prescriptions for patient age group (25-64 years of age) relatively remained consistent.

Total number of Cymbalta® (duloxetine HCl) prescriptions in age group 0-17 years and 18-24 years of age increased but the percent share gradually decreased in both age groups. In patient age group 0-17 years of age, the total number of Cymbalta® (duloxetine HCl) prescriptions increased from approximately 53 thousand in year 2005 to approximately 94 thousand in year 2009 but the percent share of total Cymbalta® (duloxetine HCl) prescriptions for patient age group 0-17 years of age gradually decreased from 1.1% in year 2005 to 0.6% in year 2009.

Similarly, in patient age group 18-24 years of age the total number of Cymbalta® (duloxetine HCl) prescriptions increased from approximately 162 thousand in year 2005 to approximately 345 thousand prescriptions in year 2009, but the percent share of total Cymbalta® (duloxetine HCl) prescriptions for patient age group 18-24 years old gradually decreased from 3.3% in year 2005 to 2.4% in year 2009.

In contrast, in patient age group 65 years of age and above, total number of Cymbalta® (duloxetine HCl) prescriptions increased from approximately 758 thousand prescriptions in year 2005 to approximately 2.8 million prescriptions in year 2009 (approximately 3.5 fold increase); the percent share also increased from 13% in year 2005 to 19% in year 2009. In all age groups, Cymbalta® (duloxetine HCl) 60mg strength was the most commonly dispensed throughout the study period of year 2004 through year 2009 (table 3 in *Appendix 1*).

4.3 OUTPATIENT DISPENSED PRESCRIPTIONS FOR CYMBALTA® (DULOXETINE) STRATIFIED BY SEX

Table 4 in *Appendix 1* displays the total number of projected dispensed prescriptions of Cymbalta® (duloxetine HCl) by patient sex and drug strength in U.S. outpatient pharmacies in year 2004 through year 2009. Female patients accounted for approximately three-quarters and male patients accounted for approximately one-quarter of total Cymbalta® (duloxetine HCl) prescriptions in year 2004 through year 2009. Total number of Cymbalta® (duloxetine HCl) prescriptions in females increased from approximately 3.5 million prescriptions in year 2005 to approximately 10.8 million (3 fold increase) in year 2009. Similarly, total number of Cymbalta® (duloxetine HCl) prescriptions in males increased from approximately 1.3 million prescriptions in year 2005 to approximately 3.8 million (3 fold increase)

in year 2009. In females and males, the most common strength of Cymbalta® (duloxetine HCl) dispensed was 60mg followed by 30mg and 20 mg in year 2004 through year 2009.

4.4 NUMBER OF PATIENTS RECEIVING PRESCRIPTIONS FOR CYMBALTA® (DULOXETINE HCL)

Table 5 in *Appendix 1* displays the total number of projected unique patients receiving a dispensed prescription of Cymbalta® (duloxetine HCl) from outpatient retail pharmacies in year 2004 through 2009. Trends for patient data were similar to prescription data. Approximately 1.4 million unique patients received a prescription for Cymbalta® (duloxetine HCl) in year 2005. The number of unique patients increased to 2.8 million patients in year 2009 (increased by 2 fold from year 2005).

4.5 DISPENSED PRESCRIPTIONS BY PRESCRIBER SPECIALTY

Figure 1 in *Appendix 1* shows the number of dispensed prescriptions of Cymbalta® (duloxetine HCl) by top prescribing specialties for an aggregate time period from approval in August 2004 through April 2010. “General Practice/Family Medicine/Osteopathy” (28%) group was the top prescribing specialty for Cymbalta® (duloxetine HCl), followed by “Psychiatry” (24%), “Internal Medicine” (17%) and “Nurse Practitioners” (6%).

“Neurologist” (4%), “Physician Assistants” (2%), “Anesthesiologist” (2%), “Rheumatologists” (2%), and “Physical Medicine and Rehabilitation Specialist” (2%) were also in the top 10 groups of prescribers.

4.6 DIAGNOSES ASSOCIATED WITH THE USE OF CYMBALTA® (DULOXETINE)

Table 6 in *Appendix 1* displays the diagnosis (ICD-9) associated with the use of Cymbalta® (duloxetine HCl) for an aggregate time period from approval time in August 2004 through April 2010. According to the office-based physician practices in the U.S., approximately one-third (33%) of the diagnosis codes recorded that were associated with Cymbalta® (duloxetine HCl) use were for labeled indications such as “Major depressive disorder, single episode” (ICD-9 296.2), “Major depressive disorder, recurrent episode”(ICD-9 296.3), “Generalized Anxiety Disorder” (ICD-9 300.02), “Fibromyalgia” (ICD-9 729.1) and “Diabetic Peripheral Neuropathy” (ICD-9 250.6 and 357.2). Approximately two-thirds (67%) of the diagnosis codes recorded that were associated with Cymbalta® (duloxetine HCl) use were for off-labeled indications. Of all the diagnoses, “Depressive Disorder, not elsewhere specified” (ICD-9 311.0) was the most common diagnosis code recorded that was associated with Cymbalta® (duloxetine HCl) use (29.5%). Approximately 7.3% of the diagnosis codes were associated with “diseases of musculoskeletal system and connective tissue” (ICD-9 codes 710-739) which includes chronic pain conditions such as arthritis and back pain, and approximately 6.5% of the diagnosis codes were associated with “headaches and nerve pain” (ICD-9 codes 337-359) which includes “Chronic Pain Syndrome” (ICD-9 338.4) and “Chronic Pain, NOS” (ICD-9 338.2).

5 DISCUSSION

Based on these findings, patients with “diseases of musculoskeletal system and connective tissue” (ICD-9 codes 710-739) (7.3% of total diagnosis codes) could translate into approximately 200 thousand patients for year 2009 and a total of approximately 1 million prescriptions of Cymbalta® (duloxetine HCl) for year 2009. Adding in patients with “headaches and nerve pain” (ICD-9 codes 337-359) (6.5% of total diagnosis codes), an additional 200 thousand patients and 1 million prescriptions may be exposed for these off-labeled pain conditions.

The greatest proportion of prescribing are from General Practice/Family Medicine/Osteopathy physicians; however, specialists such as anesthesiologists and rheumatologists were among the top 10 prescribers of Cymbalta® (duloxetine HCl), albeit in lower proportions. Hence, the approval of a chronic pain indication may increase prescribing levels from these specialists.

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that Cymbalta® (duloxetine HCl) is distributed primarily to the retail outpatient setting based on the IMS Health, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these outpatient retail pharmacy channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

This review analyzed data from the outpatient retail pharmacy setting only, which accounts for approximately 76% of the total distribution volume of the selected sales market. Up to 24% of the total distribution volume going into mail order and non-retail settings was not analyzed.

SDI uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

Indications for use were obtained using SDI's PDDA, a monthly survey of 3,200 office based physicians. Although PDDA data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. In general, PDDA data are best used to identify the typical uses for the products in clinical practice, and the VONA outpatient prescription data to evaluate trends over time.

Unique patient counts may not be added across time periods due to the possibility of double counting those patients who are receiving treatment over multiple periods in the study. For this reason, summing across time periods or patient age bands is not advisable and will result in overestimates of patient counts.

6 CONCLUSIONS

Using the strictest definitions for labeled indications, we estimate that nearly two-thirds of use for Cymbalta® (duloxetine HCl) may be used off-label and that nearly 14% of drug use may be used for off-labeled pain conditions such as "diseases of musculoskeletal system and connective tissue" (7.3%) and "headaches and nerve pain" (6.5%). Approving the use of Cymbalta® (duloxetine HCl) for chronic pain may increase the patient exposure and physician prescribing to an area that is already not uncommon.

APPENDIX 1: Tables and Figures

TABLE 1

Total number of prescriptions for Cymbalta® (duloxetine) by strength dispensed in U.S. outpatient retail pharmacies, 2004-2009												
	2004		2005		2006		2007		2008		2009	
	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%
duloxetine hcl	558,214	100.0%	4,938,368	100.0%	8,520,352	100.0%	12,550,576	100.0%	14,421,962	100.0%	14,653,155	100.0%
60MG	352,744	63.2%	3,223,246	65.3%	5,558,893	65.2%	8,228,121	65.6%	9,582,886	66.4%	9,844,284	67.2%
30MG	162,670	29.1%	1,366,057	27.7%	2,409,118	28.3%	3,570,072	28.4%	4,095,101	28.4%	4,141,517	28.3%
20MG	42,800	7.7%	349,065	7.1%	552,341	6.5%	752,383	6.0%	743,975	5.2%	667,354	4.6%

Source: SDI: Vector One® National, data extracted 06-2010, Source: VONA 2010-1208 _Duloxetine_ Strength_6-23-10(1).xls

TABLE 2

Total number of prescriptions for Cymbalta® (duloxetine) by age dispensed in U.S. outpatient retail pharmacies, 2004-2009												
	2004		2005		2006		2007		2008		2009	
	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%
duloxetine hcl	558,193	100.0%	4,938,356	100.0%	8,520,338	100.0%	12,550,542	100.0%	14,421,940	100.0%	14,653,155	100.0%
0-17	7,759	1.4%	53,169	1.1%	71,298	0.8%	91,878	0.7%	94,588	0.7%	93,985	0.6%
18-24	22,117	4.0%	161,709	3.3%	239,640	2.8%	336,000	2.7%	372,125	2.6%	345,567	2.4%
25-64	447,741	80.2%	3,901,798	79.0%	6,785,356	79.6%	9,984,362	79.6%	11,392,930	79.0%	11,393,821	77.8%
65+	73,404	13.2%	757,771	15.3%	1,383,165	16.2%	2,097,603	16.7%	2,525,154	17.5%	2,785,368	19.0%
UNSPEC	7,172	1.3%	63,909	1.3%	40,879	0.5%	40,699	0.3%	37,143	0.3%	34,413	0.2%

Source: SDI: Vector One® National, data extracted 07-2010, Source: VONA 2010-1208 _Duloxetine_age_07-02-10(1).xls

TABLE 3

Total Number of Prescriptions for Cymbalta® (Duloxetine) by age and strength dispensed in U.S. Outpatient Retail Pharmacies, 2004-2009												
	2004		2005		2006		2007		2008		2009	
	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%
duloxetine hcl	558,193	100.0%	4,938,356	100.0%	8,520,338	100.0%	12,550,542	100.0%	14,421,940	100.0%	14,653,155	100.0%
0-17	7,759	1.4%	53,169	1.1%	71,298	0.8%	91,878	0.7%	94,588	0.7%	93,985	0.6%
60MG	3,910	50.4%	27,990	52.6%	35,644	50.0%	44,696	48.6%	46,558	49.2%	45,460	48.4%
30MG	3,178	41.0%	18,904	35.6%	25,963	36.4%	33,915	36.9%	34,210	36.2%	34,296	36.5%
20MG	671	8.6%	6,275	11.8%	9,691	13.6%	13,267	14.4%	13,820	14.6%	14,230	15.1%
18-24	22,117	4.0%	161,709	3.3%	239,640	2.8%	336,000	2.7%	372,125	2.6%	345,567	2.4%
60MG	14,043	63.5%	103,484	64.0%	147,019	61.3%	203,791	60.7%	226,192	60.8%	213,312	61.7%
30MG	6,595	29.8%	45,787	28.3%	72,632	30.3%	104,242	31.0%	117,056	31.5%	109,162	31.6%
20MG	1,479	6.7%	12,438	7.7%	19,989	8.3%	27,967	8.3%	28,877	7.8%	23,094	6.7%
25-64	447,741	80.2%	3,901,798	79.0%	6,785,356	79.6%	9,984,362	79.6%	11,392,930	79.0%	11,393,821	77.8%
60MG	290,825	65.0%	2,620,591	67.2%	4,544,849	67.0%	6,719,519	67.3%	7,764,883	68.2%	7,855,110	68.9%
30MG	124,818	27.9%	1,025,811	26.3%	1,831,760	27.0%	2,711,531	27.2%	3,092,338	27.1%	3,070,308	26.9%
20MG	32,098	7.2%	255,396	6.5%	408,747	6.0%	553,312	5.5%	535,709	4.7%	468,404	4.1%
65+	73,404	13.2%	757,771	15.3%	1,383,165	16.2%	2,097,603	16.7%	2,525,154	17.5%	2,785,368	19.0%
60MG	39,841	54.3%	430,907	56.9%	805,432	58.2%	1,233,119	58.8%	1,519,722	60.2%	1,706,889	61.3%
30MG	25,459	34.7%	255,461	33.7%	466,011	33.7%	708,823	33.8%	841,325	33.3%	917,966	33.0%
20MG	8,104	11.0%	71,403	9.4%	111,722	8.1%	155,661	7.4%	164,107	6.5%	160,513	5.8%
UNSPEC	7,172	1.3%	63,909	1.3%	40,879	0.5%	40,699	0.3%	37,143	0.3%	34,413	0.2%
Source: SDI, Vector One ® National: Years 2004-2009, Extracted July 2010 File Name: VONA 2010-1208 Duloxetine age strength07-06-10(1).xls												

Source: SDI, Vector One © National: Years 2004-2009, Extracted July 2010 File Name: VONA 2010-1208 Duloxetine age strength07-06-10(1).xls

TABLE 4

Total number of prescriptions for Cymbalta® (duloxetine) by gender and strength dispensed in U.S. outpatient retail pharmacies, 2004-2009												
	2004		2005		2006		2007		2008		2009	
	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%
duloxetine hcl	558,193	100.0%	4,938,356	100.0%	8,520,338	100.0%	12,550,542	100.0%	14,421,940	100.0%	14,653,155	100.0%
Female	399,235	71.5%	3,543,509	71.8%	6,255,842	73.4%	9,237,412	73.6%	10,611,428	73.6%	10,808,676	73.8%
60MG	251,798	63.1%	2,305,457	65.1%	4,056,619	64.8%	6,020,456	65.2%	7,008,177	66.0%	7,224,304	66.8%
30MG	116,554	29.2%	984,487	27.8%	1,786,265	28.6%	2,651,702	28.7%	3,042,666	28.7%	3,083,117	28.5%
20MG	30,883	7.7%	253,565	7.2%	412,958	6.6%	565,254	6.1%	560,585	5.3%	501,254	4.6%
Male	150,550	27.0%	1,311,602	26.6%	2,222,472	26.1%	3,268,272	26.0%	3,762,639	26.1%	3,793,474	25.9%
60MG	96,012	63.8%	864,373	65.9%	1,475,270	66.4%	2,178,255	66.6%	2,542,543	67.6%	2,585,599	68.2%
30MG	43,072	28.6%	356,796	27.2%	610,465	27.5%	905,397	27.7%	1,038,478	27.6%	1,043,723	27.5%
20MG	11,466	7.6%	90,433	6.9%	136,737	6.2%	184,620	5.6%	181,618	4.8%	164,152	4.3%
UNSPEC	8,408	1.5%	83,245	1.7%	42,024	0.5%	44,858	0.4%	47,873	0.3%	51,005	0.3%

Source: SDI: Vector One® National, data extracted 07-2010, Source: VONA 2010-1208 _Duloxetine_gender_strength_07-02-10(1).xls

Source: SDI, Vector One© National, data extracted 07-2010, Source: VONA 2010-1208 _Duloxetine_gender_strength_07-02-10(1).xls

TABLE 5

Total number of unique patients receiving a dispensed prescription for Cymbalta® (duloxetine) from U.S. outpatient retail pharmacies, Years 2004-2009

	Years					
	2004	2005	2006	2007	2008	2009
Unique Patients*	318,651	1,408,766	2,103,719	2,729,110	2,966,302	2,828,372

*Do not add across years, summing across years will result in double counting and overestimates of patient counts. SDI, Total Patient Tracker, Year 2004-2010, Extracted June 2010

FIGURE 1

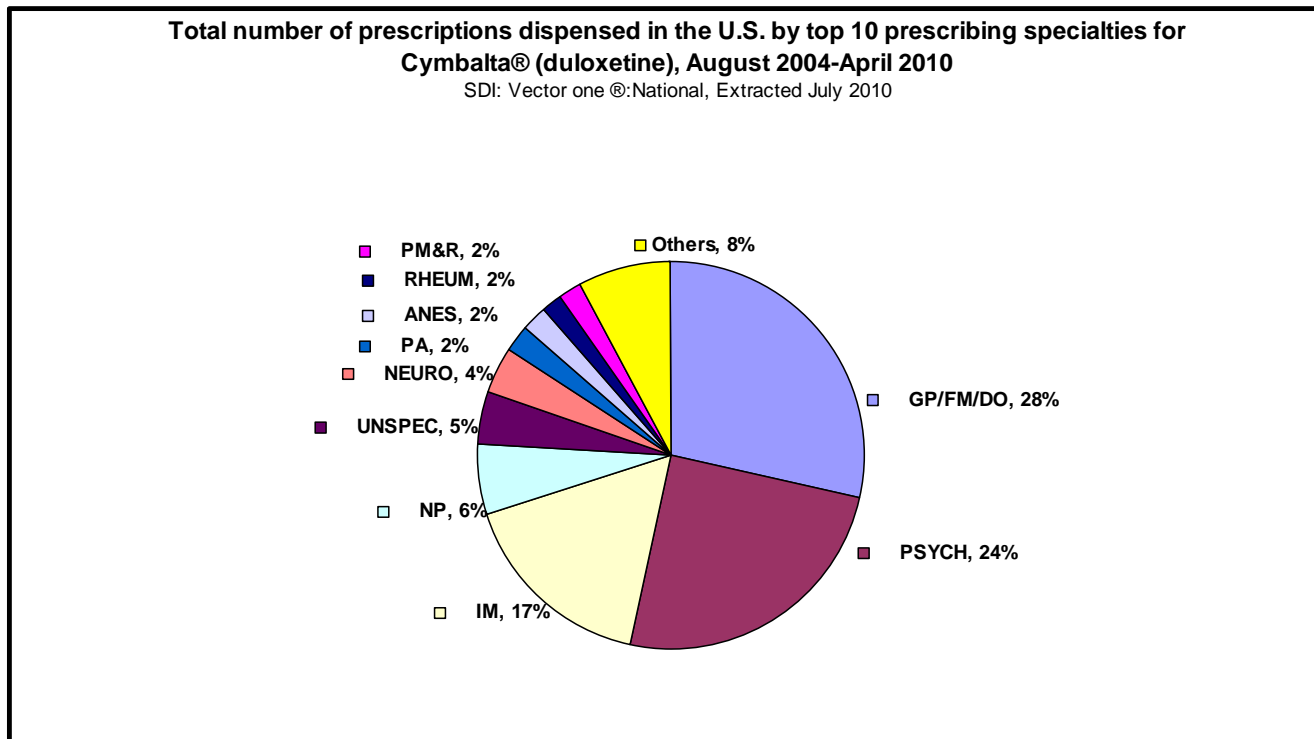


TABLE 6

Diagnosis associated with use (by grouped ICD-9 codes) for Cymbalta® (duloxetine HCl) as reported by office-based physicians in the U.S., August 2004-April 2010

August 2004- April 2010			
		Uses (000)	Share %
Total Cymbalta Market		30,902	100.0%
Labeled Indications	ICD-9		33%
Diabetic Peripheral Neuropathy (DPN)	357.2 and 250.6	1,524	4.9%
Major Depressive Disorder (MDD)	296.2 and 296.3	6,321	20.5%
Generalized Anxiety Disorder (GAD)	300.02	589	1.9%
Fibromyalgia (FM)	729.1	1,845	6.0%
Unlabeled Indications			67%
Other Psych Disorders (excluding MDD and GAD)		15272	49.4%
Neoplasms (140-239)		24	0.1%
Headaches and Nerve Pain (337-359, excluding 357.2)		1996	6.5%
Diseases of the musculoskeletal system & connective tissue (710-739, excluding 729.1)		2258	7.3%
Fever & General Symptoms (780-789)		394	1.3%
Fractures, Sprains, Contusions, Injuries (800-999)		96	0.3%
All Others		624	2.0%

Source: SDI, Physicians Drug and Diagnosis Audit, 08/04-04/09, Extracted 6/10, File: PDDA 2010-1208 Cymbalta Dx6 07-7-10.xls

APPENDIX 2: DATABASE DESCRIPTIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

SDI Vector One®: National (VONA)

SDI's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2.0 billion prescription claims per year, representing over 160 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients.

Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the database account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. SDI receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

SDI Vector One®: Total Patient Tracker (TPT)

SDI's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems. Vector One® receives over 2 billion prescription claims per year, which represents over 160 million patients tracked across time.

SDI Physician Drug & Diagnosis Audit (PDDA) with Pain Panel

SDI's Physician Drug & Diagnosis Audit (PDDA) with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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NDA-22516	ORIG-1	ELI LILLY AND CO	CYMBALTA

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RAJDEEP K GILL
07/13/2010

LAURA A GOVERNALE
07/13/2010
Cleared for background package.

Review of Clinical Data

NDA: 21-427
Drug Name: Generic Name: Duloxetine
Trade Name: Cymbalta®
Sponsor: Lilly
Material Reviewed: AERS spontaneous reports of severe hepatotoxicity with nefazodone, notes on January 22, 2010 meeting with Lilly, narratives and laboratory data for cases of marked elevation of marked liver enzyme elevation in duloxetine clinical trials
Reviewer: Marc Stone, MD
Date Completed: 4/29/2010

The purpose of this review is to summarize my opinions and recommendations concerning duloxetine hydrochloride (Cymbalta®) subsequent to discussions with the sponsor after my last review. My opinion is based upon six lines of evidence:

I. Clinical Trial Data

Laboratory and clinical trial data provide ample evidence of liver injury attributable to duloxetine. The incidence of elevated levels of ALT and AST was considerably higher during duloxetine treatment than with placebo or pretreatment, particularly at higher thresholds such as ten times the upper limit of normal. The incidence also appears to have a dose-response pattern. ALT elevation greater than ten times the upper limit of normal during treatment occurred in 46 of over 22,000 subjects exposed to duloxetine (0.2%).

The sponsor agrees with this description but argues that these elevations are self-limited and that most subjects who experienced elevations of ALT saw these levels decline and even return to normal while continuing to take the drug. I found their evidence to be unpersuasive. First, the number of subjects for whom the sponsor claims an observed decline in ALT during continuation of therapy closely matches the number of duloxetine subjects who would have experienced elevation of ALT if duloxetine were no different than placebo in its effect on liver enzymes. For example, if the incidence with duloxetine of an ALT level of 100 IU or higher were 50% greater than the incidence with placebo, then two-thirds of the cases observed in duloxetine subjects would likely not be due to duloxetine while if the incidence were 200% greater then one third of the cases observed in duloxetine subjects were likely not due to duloxetine. The sponsor's claim matches this pattern: the higher the ALT level, the higher the incidence for duloxetine subjects relative to placebo subjects and the lower the proportion of duloxetine subjects who saw a decline in ALT levels from the maximum value as the drug was continued. In summary, the data do not support the idea that elevations in liver enzymes due to duloxetine are mostly self-limited; most duloxetine subjects with elevated ALT levels who realized a reduction from maximum values while the drug was continued likely had a cause other than duloxetine for the elevation.

Second, I directly examined all of the cases in the clinical trial database of duloxetine subjects with elevations of ALT to greater than ten times the upper limit of normal for which clinical narratives were available (30 cases). Of these thirty cases, nine (30%) showed some reduction in ALT levels from maximum levels while duloxetine was continued. The incidence of such elevations was about ten times more common among duloxetine subjects than among placebo subjects, so the expected number of cases among the thirty with elevations attributable to a cause other than duloxetine would be three but the 95% confidence interval would include up to ten cases. Of these nine cases:

One case resolved with dosage reduction.

Two cases showed dramatic improvement without discontinuation or within one day after discontinuation but in each case the elevation was likely due to cholelithiasis.

One case showed a 17% decline from the maximum value (1038 IU/L to 862 IU/L) after 3 days, more suggestive of a fluctuation in levels rather than a decline.

One case showed a 40% decline from the maximum value after 6 days (1 day after discontinuation) but there was no attempt to rule out another cause (viral, autoimmune, other drugs, alcohol, etc.).

One case showed a 30% decline from the maximum value after 6 days (1 day after discontinuation) but there was no attempt to rule out another cause.

One case showed substantial improvement (decline to less than 50% of maximum values) before discontinuation without an attempt to rule out another cause.

One case had values return to normal while continuing duloxetine and some effort was made to rule out another cause. The maximum value, however, barely exceeded 10 times the upper limit of normal (10.2).

One case showed a 27% decline from the maximum value after 6 days (1 day after discontinuation).

Many of the thirty cases were symptomatic, as were a number other subjects whose maximum ALT levels fell short of ten times the upper limit of normal. Common symptoms included fatigue, nausea and anorexia. Jaundice or other indicators of hepatic failure were rare. Two cases met the criteria for Hy's Rule: elevation of ALT, AST and total bilirubin without evidence of obstruction or cholestasis, such as elevation of alkaline phosphatase. One of these cases showed strong evidence of viral hepatitis. In the other, there was a history of spasmodic abdominal pain and cholelithiasis was suspected. Abdominal ultrasound was negative and the minimal elevation of alkaline phosphatase relative to much larger transaminase elevations along with a plausible alternative explanation for abdominal pain (post-surgical adhesions) make cholelithiasis an unlikely explanation. The subject did, however, present with surgically confirmed cholelithiasis six months later. It was not confirmed, however, as to whether this incident presented with a similarly atypical biochemical pattern as was seen in the initial episode.

II. Retrospective Cohort Study

Data from a retrospective cohort study limited to serious conditions documented on medical records showed an excess incidence of potentially serious liver injury¹ during

¹ defined as hepatic failure, non-infectious fulminant hepatitis or acute hepatitis, hepatic encephalopathy or hepatic coma, liver transplant, hepatic necrosis, toxic liver disease, toxic hepatitis, jaundice/icterus or

the first 90 days of duloxetine treatment that could be conservatively estimated to be one case per 4000 patient exposures.

The sponsor commissioned a retrospective cohort study based upon insurance claims data to compare the incidence of potentially serious liver injury in patients prescribed duloxetine to a series of propensity score matched comparator groups. Lilly submitted the study report to FDA, concluding that the incidence of such events was no higher with duloxetine than it was among comparators. My review of this study identified a number of issues in their analysis, most of which served to reduce the power to detect a difference. The most questionable assumption made by the study's primary analysis was that risk for drug induced liver injury was constant no matter how long exposure was continued; it would be more consistent with the usual clinical pattern of drug-induced liver injury to limit the primary analysis to the first 90 days of treatment. I also noted that each of the five comparator groups had a lower incidence of potentially severe liver injury than duloxetine over the first 90 days of observation, the differences in comparison to duloxetine were similar in magnitude for all comparators, and that four of the five comparisons fell just short of statistical significance. I concluded that such a consistent pattern made it appropriate to look at a pooled estimate of the effect of duloxetine over these comparisons that the pooled estimate indicated that the observed effect was unlikely to be due to chance. In discussion with the sponsor, I confirmed to them that the pooled result was robust and statistically significant over a large variety of assumptions and statistical techniques.

Lilly contended that many of the cases contributing to the excess risk from duloxetine were identified on the basis of an elevation of AST or ALT rather than any of the other serious conditions included in the study's case definition. They argued that, despite the term, "potentially severe liver injury", these elevations should be considered benign and self-limited based on what was seen in subjects with similar elevations in clinical trials. As I noted in my discussion of the clinical trial data, I do not believe there is much evidence that large elevations in AST or ALT caused by duloxetine will usually resolve despite continuation. Furthermore, unlike the situation in clinical trials, these cases of large AST or ALT elevations are not recognized as a result of constant monitoring; in many cases patients were sufficiently symptomatic to seek medical attention.

Lilly also contended that cases counted as contributing to the excess risk from duloxetine for reasons other than AST or ALT elevations were due to co-morbidity. The matching process used in this study should have assured a similar incidence of co-morbidity in the comparator groups. It is the sponsor's contention that matching process failed and that the choice to prescribe duloxetine is confounded positively with pre-existing or coincident liver disease from other causes (despite current labeling intended to discourage its use in patients with liver disease). This seems unlikely because the matching process appeared to be quite aggressive in excluding duloxetine patients if comparator patients with comparable co-morbidity could not be found. Between 30% and 80% of duloxetine-

ascites, hepatectomy or other liver operations, coagulation factor V deficiency due to liver disease, acquired hypoprothrombinemia, (INR>1.5 and prothrombin time< 50%, or drug-induced coagulation factor deficiencies), hyperbilirubinemia or total bilirubin>5 mg/dl, or AST and ALT >500 IU/L

treated patients were excluded because a comparable patient could not be found within a given comparator group. Synergy is a more parsimonious and reasonable alternative explanation: duloxetine worsened co-morbid disease that was otherwise not severe enough to meet the case definition.

Lilly has proposed doing another study similar to this one but with the exclusion of patients with pre-existing liver disease and removing elevation of AST or ALT levels to more than 500 IU/L from the case definition. Although the sample size is larger, its power is insufficient. The study is likely to detect a statistically significant difference in incidence between duloxetine and a comparator group only if the true difference incidence is greater than one in 3000 patients. The events described in the case definition would still be of considerable concern even if they occurred at a rate much lower than this. Events that did occur at a rate detectable in the proposed study are likely to have already been recognized in the clinical trial database which contains over 30,000 subjects.

III. Number of AERS Reports

There have been more than one thousand cases of liver injury associated with duloxetine reported in AERS. Relative to prescription volume reporting rates for duloxetine have been three to eight times higher than those observed with other antidepressants (other than nefazodone).

The sponsor has made two arguments in response. First, Lilly believes that most of the reports of liver injury are concerned with minor elevations of AST and ALT that are clinically insignificant. I agree but would also point out that this is also true for reports of liver injury with other antidepressants. Remove the clinically insignificant reports from both groups and the relative incidence of more serious hepatic events is likely much the same. Second, the sponsor has argued that the high rate of occurrence of liver-related adverse events in duloxetine patients is a result of duloxetine being used in a population with higher co-morbidity than the population of users of other antidepressants. My examination of the most serious AERS reports for duloxetine (cases either with jaundice or with AST or ALT >500 IU/L) showed that this did not account for the difference: the great majority of reported cases occurred in middle-aged adults with psychiatric indications without substantial co-morbidity, pre-existing liver disease, or alcoholism.

IV. Blinded Review

Relative to prescription volume, AERS reports of hepatic failure are six times more common with duloxetine than with paroxetine; the rate for duloxetine is similar, or perhaps slightly lower, in magnitude to the reporting rate for nefazodone. This difference persisted when cases series of reports of hepatic failure for these three drugs were reviewed by a blinded panel and cases thought to be unlikely to be drug-related were excluded, indicating that duloxetine cases reported to AERS are no more likely to be confounded by co-morbidity, concomitant medication or poor documentation than case reports concerning other antidepressants.

The only concern raised by the sponsor to this observation was that the case definition for “hepatic failure” was quite broad so most of the cases were not life-threatening. However, the number of cases that appeared to be life-threatening was too small to allow a meaningful result. Very serious cases, such as those leading to death or transplant, occur too infrequently to be considered quantitatively.

V. Disproportionality Analysis

“Data-mining” scores for duloxetine for hepatotoxicity-related terms, including jaundice and hepatic encephalopathy, have climbed steadily since the drug came to market. They are similar to those for nefazodone and clearly exceed levels seen with other antidepressants.

The sponsor associates these findings with the recognized ability of duloxetine to cause elevations of AST and ALT levels. These findings, however, are not limited to transaminase levels; they include less equivocal indicators of significant liver injury such as jaundice and elevation of blood ammonia.

VI. Analysis of Case Reports

There have been more than a dozen reports that strongly implicate duloxetine as the cause of acute non-fatal hepatic failure: hepatocellular damage severe enough to cause jaundice in the absence of obstruction (Hy’s Law). There have been several cases of death from hepatic failure while taking duloxetine that could plausibly be due to this drug but where other causes could not be ruled out. There are also a number of cases that show duloxetine to be the likely cause of severe cholestatic injury.

The sponsor has argued that there have been no “clean” cases of duloxetine hepatotoxicity resulting in death or transplant. One of their consultants stated, on the basis of his (10 year-old) recollection, in the case of nefazodone there had been a number of “clean cases”. Lilly argued that, despite considerable similarities between nefazodone and duloxetine in regard to lesser degrees of hepatotoxicity, the two drugs were substantially different in their potential to cause hepatic failure severe enough to lead to death or transplant.

I have located the reviews and case reports that led to the decision to require a boxed warning for hepatotoxicity for nefazodone. This decision was based upon five (or six) cases resulting in death or transplant (In the sixth case it is unclear whether the patient recovered without a transplant.):

1. A 54 y/o woman who did not develop signs of liver disease until more than seven months on the drug (somewhat long for onset). She had also been taking clorazepate, which had been associated with mild elevation of liver enzymes but no severe liver damage. Biopsy showed submassive centrilobular (zone 3) necrosis with collapse of the hepatic framework and adjacent ductular proliferation with cholestasis.
2. A 16 y/o girl developed liver failure 16 weeks after beginning nefazodone. Results of serological examinations for were not reported. Pathological examination showed extensive centrilobular necrosis and lobular collapse with

cholestasis and ductular proliferation, as well as ballooning of hepatocytes accompanied by lymphocytic infiltrates.

These first two cases were in a published report (Aranda-Michel J *et al.* Nefazodone-Induced Liver Failure. *Ann Intern Med.* 1999; 130:285-288) from a university transplant center and are the cleanest and best documented. They considered nefazodone to be the most likely cause but could not rule out an unidentified viral agent; viral serologies were not reported. It should also be noted that nefazodone was not approved for use in adolescent patients, so its use in the second case was off-label and possibly inappropriate.

3. An 80 y/o woman presented with jaundice after seven weeks of nefazodone. She had also been taking estrogen. Serologic tests for hepatitis A and B were negative (no mention of hepatitis C) but no immunological studies were reported and no pathology specimens were obtained.
4. A 44 y/o woman developed hepatic failure after four months of nefazodone treatment. She showed serological evidence of immunological liver disease (anti-histone and antimitochondrial antibodies). Pathological examination was non-specific and gave no indication of the underlying cause.
5. A 57 y/o woman developed hepatic failure after four months of nefazodone and three months of trifluoperazine (phenothiazines are associated with hypersensitivity reactions and acute hepatic failure) and oxazepam. She gave a history of alcohol consumption of two or three drinks per day. Pathological examination showed established cirrhosis without specific features to indicate etiology.
6. A 47 y/o diabetic woman became jaundiced after about two weeks of nefazadone. She had also been taking methadone, doxepin and insulin. No alcohol use or significant acetaminophen use. No serological or pathological reports were available.

In these four cases, nefazodone is a plausible cause for liver failure but there is either insufficient detail or too much evidence for other causes to be confident.

For duloxetine, there is one published case resulting in death (Hanje AJ *et al.* Case Report: Fulminant Hepatic Failure Involving Duloxetine Hydrochloride, *Clinical Gastroenterology and Hepatology*, 4(7):912-917) from a university transplant center:

1. A 56 year old woman had been taking duloxetine 30mg for one year. Four weeks after the dose was increased to 60 mg daily (and was given mirtazapine 15 mg (PRN?) for insomnia, she developed jaundice. Obstruction was ruled out through ERCP. The patient carried no prior history of chronic liver disease. A complete work-up for alternate causes failed to reveal another explanation. Liver biopsy showed moderate amounts of microsteatosis and macrosteatosis and hepatocellular cholestasis. There was ballooning degeneration of hepatocytes with bridging necrosis and centrilobular hepatocyte dropout. Although non-specific, these histologic changes were consistent with subacute liver injury.

We have also received an unpublished paper from another university transplant center (Chalasani N *et al.* Severe Liver Injury after Initiating Therapy with Duloxetine (Cymbalta) in Two Adults) detailing two severe but non-fatal cases that the authors believed to be caused by duloxetine: “Within few weeks after receiving duloxetine, both patients presented with symptomatic liver injury. One patient exhibited “pseudo-

acetaminophen” pattern of liver injury with very high aminotransferases, toxic zonal necrosis, and acute renal failure. The liver injury was mixed hepatocellular/cholestatic with “pseudomononucleosis” pattern in the second patient. Extensive work-up revealed no competing etiologies. In both patients, liver injury gradually improved upon discontinuing duloxetine.”

I have also reviewed six other fatal duloxetine cases that are similar to the four unpublished nefazodone cases in that causation by duloxetine/nefazodone is plausible but inconclusive due to inadequate information or other possible causes:

2. An 85 y/o woman who had been taking duloxetine for a year (long for onset) as well as furosemide and ergocalciferol presented with encephalopathy, jaundice and markedly elevated transaminases without evidence of obstruction. Hepatitis A, B and C serologies and blood cultures were negative. No pathological examination was available. The attending physician concluded the patient’s death was due acute liver failure from duloxetine.
3. A 77 y/o woman developed hepatic failure one month after beginning duloxetine and valproate (valproate is associated with fatal hepatic failure, but mostly in infants and small children). Viral studies were negative. No pathology was available.
4. A 76-year-old man with a history of diabetes, hypertension, cholelithiasis and peptic ulcer disease with hemorrhage and blood transfusion three months earlier. Baseline laboratory: AST 30, ALT 30, total bilirubin 0.7, alkaline phosphatase 133 and albumin 4.0. Concomitant medications included fenofibrate, atorvastatin, pantoprazole, lorazepam, metformin, valsartan, pioglitazone and folic acid. He presented with jaundice one month after beginning duloxetine. ERCP showed an ampullary mass and common bile duct stricture, the common duct was not distended and the biliary system was otherwise normal; biopsy of the ampulla showed reactive changes. The attending physician listed cause of death as "Hepatic failure, fulminant, presumed duloxetine toxicity".
5. A 62 year old woman with no history of alcohol use, viral hepatitis, gallstones or excessive acetaminophen usage. She was receiving duloxetine 120mg daily in addition to fluoxetine. On an unprovided date, the patient was jaundiced. AST and ALT were both in the 1000's; she subsequently died of acute hepatic failure. No serology or pathology was reported.
6. A 54 year-old woman with a history of rheumatoid arthritis, diabetes, hypertension, anxiety, depression, panic attacks, osteoporosis, osteoarthritis, hypertensive cardiomyopathy, nonalcoholic steatohepatitis, kidney stones, anemia, hyperlipidemia, diabetic neuropathy and cholecystectomy. She was treated for the rheumatoid arthritis with methotrexate for 20 years, etanercept, infliximab, leflunomide (two years), prednisone and pregabalin. Other concomitant medications: risperidone, fludrocortisone, lisinopril and insulin. No history of alcohol use or viral hepatitis. Immediately before starting duloxetine: bilirubin 0.7, albumin 3.6, ALT 68, AST 59 and a liver biopsy showed mild periportal and minimal portal fibrosis consistent with grade one MTX toxicity, and no ballooning hepatocytes or syncytial cells. One month after starting duloxetine she became jaundiced. CT scan, MRCP, and ultrasound did not show

- evidence of portal vein thrombosis or biliary obstruction. ANA, ASMA, ACV, HSV, EBV and hepatitis panel were negative. Liver biopsy: giant cells with Mallory's hyaline and extensive ballooning degeneration; stains for CMV, HSV 1 and 2 were negative.
7. A 42 year old woman with a history of fatty liver, dystonia, seizures and no alcohol use. Eight months after beginning duloxetine and four months after beginning sodium valproate she developed liver failure. CT scan showed moderate hepatic steatosis and no evidence of bile duct dilatation or obstruction. Hepatitis B surface antigen negative, hepatitis B core antigen negative, hepatitis A antibody negative, hepatitis C antibody negative. Antinuclear antibody and smooth muscle antibody were negative. No pathology specimens were available.

The principal differences between the nefazodone cases and the duloxetine cases is that the duloxetine cases generally seem to have more concomitant medications and, in some cases, pre-existing but stable liver disease. In most of the fatal duloxetine cases, the evidence for duloxetine as the cause is circumstantial: there are numerous well-documented “clean cases” of severe *non-fatal* hepatic injury with duloxetine and a number of fatal cases that are not so clean but occur in the right time frame to implicate duloxetine. I can see only two possibilities: 1) although duloxetine can often cause severe non-fatal liver injury it almost never has the capacity to cause fatal liver injury so the association of duloxetine with fatal cases is almost always a chance association, or 2) because duloxetine can often cause severe non-fatal liver injury it can sometimes cause fatal injury, especially in patients with pre-existing liver disease, so a significant portion of fatal cases associated with duloxetine are caused by the drug even though, because of confounding, it may be difficult to determine which cases are causal and which are coincidental. To me, the second possibility is the more plausible explanation.

Conclusions

As I stated in my last review, because the pattern of hepatotoxicity observed with duloxetine is comparable to nefazodone; the two drugs should have comparable labeling, i.e., a boxed warning. The purpose of the boxed warning is the same for both drugs: to communicate to both prescribers and patients that the drug has a serious disadvantage: it is more likely to cause a serious adverse event (hepatic failure) than other drugs indicated for the same condition. The warning should not prevent consideration of duloxetine or nefazodone when alternative treatments are contraindicated, not tolerated, or ineffective.

The need for a boxed warning could be discounted if a drug were also to have significant advantages over alternatives, either less risk of other important adverse events or greater chance of therapeutic success. Nefazodone does have such a countervailing advantage (lower risk of sexual dysfunction). For psychiatric indications, duloxetine does not have any well-established advantages. Its distinguishing characteristic, causing both serotonin and norepinephrine reuptake inhibition, is theoretical and has yet to be shown to have clinical significance. Furthermore, this characteristic is shared with two other drugs, venlafaxine and desvenlafaxine.

Duloxetine is also indicated for symptom relief in two conditions, fibromyalgia and diabetic neuropathy and is being considered for an indication for treatment of chronic pain. For fibromyalgia and diabetic neuropathy, highlighting the risk of severe hepatic injury with duloxetine is likely to aid decision-making as to whether duloxetine is a better choice than alternative treatments. For chronic pain, duloxetine does hold out the prospect of reducing the use of conventional analgesic drugs (opioids, acetaminophen and non-steroidal anti-inflammatory drugs) which, at high doses, probably present greater risks to patients than duloxetine does. At low doses, however, these analgesic drugs are relatively benign. If duloxetine is used as an alternative to these drugs at lower doses, safety is likely not increased and plausibly could worsen; a boxed warning would probably discourage such usage. If duloxetine is used as an adjunct when maximum dosages of other drugs have been achieved, a therapeutic benefit may be obtained but safety is not increased: the prospect of therapeutic benefit would need to be weighed against the risk of liver injury, a decision process that again would be aided by a boxed warning. The only situation where safety is likely to be increased with the use of duloxetine is when a physician is considering going from a lower to a higher dose and is sufficiently concerned about the risk that adjunctive duloxetine might be considered a safer alternative. Those physicians thoughtful enough to seriously consider the risks of conventional analgesics in these circumstances are unlikely to overreact to the boxed warning.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21427	ORIG-1	ELI LILLY AND CO	CYMBALTA(DULOXETINE HCL)20,30,40,60MG

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/s/

MARC B STONE
04/29/2010

VICTOR D CRENTSIL
04/29/2010

Dr. Stone recommends a boxed warning for duloxetine; however, in my opinion, at the moment, there is no evidence for the need for a boxed warning for duloxetine. The current labeling for duloxetine provides information on the hepatotoxicity of duloxetine. Dr. Stone's review does not provide a persuasive discussion of a proposition that current labeling is inadequate or that there is a change in the characteristics of duloxetine hepatotoxicity for which a boxed warning is warranted. Please refer to my memo for details.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF PSYCHIATRY PRODUCTS
HFD-130, BUILDING 22, 10903 NEW HAMPSHIRE AVE.
SILVER SPRING, MD 20993

MEMORANDUM

DATE: May 10, 2010

SUBJECT: Covering Memorandum for Dr. Marc Stone's Reviews of the Hepatotoxicity of Duloxetine Hydrochloride (Cymbalta[®])

FROM: Victor Crentsil, M.D., M.H.S.
Deputy Director for Safety (Acting), Division of Psychiatry Products

TO: File NDA 21427

Background

This is a covering memorandum to Dr. Marc Stone's reviews of the hepatotoxicity of duloxetine hydrochloride dated 10/28/2009 and 4/29/2010. Dr. Stone recommends a box warning for hepatotoxicity for duloxetine after review of the clinical trial data, the retrospective cohort study (i3 Aperio study), the FDA blinded review, AERS reports, disproportionality analysis, and case reports. His findings were discussed at a face-to-face meeting between the Division of Psychiatry Products and Eli Lilly on 1/22/2010 (See the meeting minutes for details). It is my perspective that since the current labeling of duloxetine has information on hepatotoxicity under the Warnings and Precautions section, to institute a boxed warning, three substantive questions deserve to be answered - (i) Does the available evidence suggest that exposure to duloxetine is independently associated with severe liver injury (severe liver injury defined as irreversible liver failure that is fatal or require liver transplantation¹)? (ii) Is there a change in the characteristics of duloxetine hepatotoxicity that constitutes new hepatic safety information? (iii) Is the information on duloxetine hepatotoxicity in current labeling inadequate? The answers to all three questions are not affirmative upon my review of the evidence. Dr. Stone's reviews neither assert an independent association between exposure to duloxetine and severe liver injury nor do they show that there is a change in the characteristics of duloxetine hepatotoxicity, constituting new hepatic safety information to warrant a boxed warning. Furthermore, Dr. Stone's reviews do not demonstrate that the current duloxetine hepatotoxicity labeling provides insufficient warning. Therefore, I believe, at the moment, a boxed warning for duloxetine hepatotoxicity is not warranted.

¹ (FDA) Guidance for Industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation. July 2009

Evaluation of the Review Findings of Dr. Stone

I. Clinical Trial Data: Dr. Stone discusses the association between duloxetine exposure and liver enzyme elevations observed during clinical trials. He reports that two of the thirty cases with ALT elevations greater than ten times the upper limit of normal met criteria for Hy's law. This is incorrect because both cases had other diseases to explain their liver enzyme or total bilirubin elevations (one had viral hepatitis and the other cholelithiasis). In addition, Dr. Stone's reviews do not demonstrate that the liver enzyme elevations he reports were associated with significant clinical consequences. Such clinically inconsequential liver enzyme elevation has been described with other antidepressants. The current labeling of duloxetine mentions observations of liver enzyme elevations in clinical trials as well as the dose-dependent pattern. Therefore, Dr. Stone's reviews of the clinical trial data provide no new hepatic safety information warranting a boxed warning.

II. Retrospective Cohort Study: In my view, the results of this study do not contribute useful information for determination of the potential for duloxetine to cause severe liver injury for a variety of reasons. To mention a few, first, the total number of hepatic events were so few (<0.1% overall prevalence) that the study lacked adequate power to detect a difference between the incidence of severe liver injury attributable to duloxetine and the comparator cohorts, whether you limit the analysis to the first 90 days or not. Second, the propensity score matching was not successful; therefore, appreciable confounding (especially, confounding by indication) is likely to have persisted. Third, the marked difference between confirmation rates of hepatic events between duloxetine and all other cohorts (duloxetine-57.6% versus other cohorts-37.8%) raises concern for bias in ascertainment of hepatic events. These issues can not be mitigated by any statistical analytic approach that I am aware of.

Dr. Stone concluded that, compared to the other drugs, duloxetine was statistically significantly associated with potentially severe liver injury after a pooled analysis. Aside from concerns for the validity of the pooled analysis he performed since the patient cohorts were not independent of each other, I will not consider the pooled analysis reliable because it can not correct defects in the data introduced by a biased ascertainment of hepatic events, etc.

III. AERS reports/Disproportionality Analysis: Since this issue is beyond detecting a signal for hepatotoxicity, the value of evaluating AERS reports and performing disproportionality analysis is for monitoring for excess reporting of severe liver injury. Dr. Stone's counts of AERS reports (which seems to have been generated solely based on MedDRA terms) and disproportionality analysis were not informative because they were not limited to severe liver injury cases. Moreover, calculation of rates based on cases that have been reviewed and determined to have, at least, a probable causal link to drugs under evaluation would have added value to

the evaluation. The AERS reports and disproportionality analysis did not suggest that a change in the characteristics of duloxetine hepatotoxicity, which may constitute new hepatic safety information. Furthermore, the contribution of AERS reports and disproportionality analysis to a recommendation of a boxed warning when the retrospective cohort epidemiologic study is uninterpretable is however questionable.

IV. FDA Blinded Review: This was a blinded review of case series for duloxetine, paroxetine, and nefazodone to determine if hepatotoxicity-associated adverse event reports for duloxetine were qualitatively similar in content to those of the 2 other drugs. This review was not intended to establish a causal link between duloxetine exposure and severe liver injury; therefore, I will not discuss it any further.

V. Comparison to Nefazodone: Dr. Stone bases his recommendation, at least in part, on similarity between duloxetine and nefazodone. However, both drugs differ substantially with regard to their epidemiology of severe liver injury and pharmacology pertinent to hepatotoxicity.

Focusing on the epidemiology of severe liver injury cases, for nefazodone, at the time of the institution of the boxed warning in 2001, according to the 1/31/2003 memo of Dr. Gerard Boehm, there were 5 unconfounded cases of acute liver failure resulting in death or transplant after 1,400,000 person-years of use in 2001. This corresponds reasonably well with the 1 in 250,000 to 300,000 patient-years rate of liver failure resulting in death or transplant stated in the boxed warning of nefazodone. For duloxetine, according to the postmarketing experience document submitted by the sponsor for their chronic pain indication application, as of February 2009, there had been 6,382,000 person-years of duloxetine use, i.e., a greater than four-fold exposure to duloxetine compared to that of nefazodone at the time of the nefazodone boxed warning (current exposure to duloxetine is likely to be higher than the estimate in February 2009). As far as I am aware, there is no unconfounded case of acute liver failure resulting in death or transplant attributable to duloxetine. Therefore, duloxetine is not similar to nefazodone in its epidemiology of severe liver injury.

Duloxetine does not share the proposed hepatotoxic pharmacological property of nefazodone. Nefazodone hepatotoxicity has been proposed to be due to its inhibitory effect on bile acid transport, which may be a property exhibited by at least 2 other hepatotoxic drugs, troglitazone and bosentan.²

VI. Analysis of Case Reports: Dr. Stone admits that there were at least two “clean” cases of nefazodone severe hepatic injury at the time the boxed warning was put in place and it seems he believes there is one unconfounded case of duloxetine severe hepatic injury.

² Kostrubsky SE et al. (2006). Inhibition of hepatobiliary transport as a predictive method for clinical hepatotoxicity of nefazodone. Toxicological Science 90(2), 451-459.

Below are my comments on the duloxetine fatal case Dr. Stone believes is unconfounded:

This is the case of the 56-year-old female published by Hanje AJ et al. (2006). She is the 4th patient (Case Narrative # 5926697) discussed among the 40 hepatic death cases submitted to me by Dr. Stone in January 2010. The details on the case in the document Dr. Stone sent to me lead me to conclude that the contribution of underlying chronic liver disease including autoimmune hepatitis and cirrhosis of the liver to the patient's hepatic failure can not be excluded. First, she was reported to have liver metastasis at the initial presentation of her non-Hodgkin's lymphoma (NHL), which although may have responded to chemotherapy, is not ignorable because it makes it less likely that her liver was normal prior to exposure to duloxetine. Furthermore, a CT scan probably performed when she was hospitalized for hepatic failure commented that she may have intraperitoneal and retroperitoneal lymph nodes that were more than expected; this suggests that her NHL, which can have an indolent course, may not have completely resolved as the authors of Hanje et al. believed. Second, concern for autoimmune hepatitis stems from the report that she had an elevated gamma globulin. Third, she was reported to have changes suggestive of cirrhosis of the liver with portal hypertension on an abdominal CT scan. Finally, the contribution of mirtazapine to her liver failure remains unclear. Hence, the relationship between duloxetine exposure and her fatal hepatic failure does not appear to be unconfounded.

For the cases submitted to us by Chalasani et al., it is difficult to believe that the first case did not have alcoholic liver disease given his consumption of 6-7 drinks per day for 3-4 times a week. Also of note is his anti-smooth muscle antibody titer, which was 1:80, suggesting the need for exclusion of an autoimmune disorder that could alternatively explain his hepatitis and renal dysfunction. The second patient's presentation does not qualify as a severe liver injury. This second case may have been exposed to a toxic level of duloxetine, which the authors admit to in their discussion of the case. The pattern of liver enzyme elevation in the second case is covered under current labeling for duloxetine hepatotoxicity.

Consequently, in my view, there is no report of an unconfounded case of severe liver injury attributable to duloxetine.

- VII. The risk-benefit discussion provided by Dr. Stone in the concluding remarks for his 4/29/2010 review is invalidated by a lack of support for his premise that duloxetine is independently associated with severe hepatic injury and that it has a hepatotoxicity profile similar to that of nefazodone.

Conclusions and Recommendations

Based on my review of the data and evaluation of Dr. Stone's reviews, the following are my conclusions:

1. The results of Dr Stone's analysis of clinical trial data are represented in current labeling.
2. Dr. Stone's AERS reports and disproportionality analysis did not show a change in the characteristics of duloxetine hepatotoxicity that constitute new hepatic safety information.
3. There is no reported unconfounded case of severe liver injury attributable to duloxetine.
4. The retrospective cohort study (i3 Aperio study) did not provide information useful for a reliable conclusion on the issue of whether duloxetine use is independently associated with severe liver injury.
5. The pattern of hepatotoxicity observed with duloxetine is not comparable to that of nefazodone.

Therefore, I recommend that the current hepatotoxicity labeling for duloxetine be retained without addition of a boxed warning and surveillance for duloxetine-associated severe liver injury continued.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21427	ORIG-1	ELI LILLY AND CO	CYMBALTA(DULOXETINE HCL)20,30,40,60MG

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/s/

VICTOR D CRENTSIL
05/10/2010

**MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: May 18, 2010

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products (DPP)
HFD-130

SUBJECT: Hepatotoxicity associated with duloxetine

TO: File, NDA 21-427/Duloxetine

Background

In the U.S., Duloxetine HCl is approved under the trade name Cymbalta® for the treatment of major depressive disorder (MDD) and generalized anxiety disorder (GAD) under NDA 021427. Cymbalta has also been approved for diabetic peripheral neuropathic pain (DPNP) under NDA 021733, and for fibromyalgia (FM) under NDA 022148. An NDA for Cymbalta for patients with chronic pain (NDA 022516) is currently under review, and will be the subject of an advisory committee meeting in August, 2010.

Lilly and the FDA (Division of Psychiatry Products) have been engaged in ongoing hepatic safety discussions since duloxetine's original NDA was submitted. Even at the time of its original approval in 2004, the labeling for duloxetine noted a potential for hepatic injury. As data pertinent to hepatotoxicity have accumulated since the original approval, the labeling language regarding hepatotoxicity has undergone several revisions. The current labeling language regarding hepatotoxicity for Cymbalta is located as the second entry in the Warnings and Precautions section, and is, in my view, a fairly strongly worded statement alerting prescribers to the risk of significant liver injury with this drug. It advises prescribers to avoid use in patients with substantial alcohol use or those with evidence of chronic liver disease.

Dr. Marc Stone who is currently a clinical reviewer in DPP's safety group has been the primary clinical reviewer for the duloxetine hepatotoxicity issue since its original approval. He has written several reviews on this topic over the years, including most recently a very comprehensive review covering essentially all the accumulated data (10-28-09 review) and a much briefer update (4-29-10) covering the period since his 10-28-09 review. Dr. Victor Crentsil, DPP's deputy director for safety, has also written an overview memo regarding this issue (5-10-10).

We have met with Lilly to discuss this issue on several occasions over the years since the original approval, including most recently on 1-22-10. The purpose of that meeting was to

provide an opportunity for Dr. Stone to present findings from his most recent review of duloxetine with regard to hepatotoxicity, and to give Lilly and its consultants an opportunity to respond to his findings and arguments (see meeting minutes).

The issue that currently needs resolution is whether or not to further strengthen the labeling for duloxetine to add a box warning for hepatotoxicity. Dr. Stone has made this recommendation both in his 10-28-09 review and now subsequently in his 4-29-10 update. Lilly, of course, disagrees with this proposal, and Dr. Crentsil also disagrees (see 5-10-10 memo). In responding, I will not attempt to reconstruct Dr. Stone's arguments, or Dr. Crentsil's counter-arguments. These are thoroughly explained in each of their recent memos. I will, however, summarize certain key points that I feel are critical to making a final decision about the issue of a box warning for hepatotoxicity.

Dr. Stone's Case for a Box Warning and Counter-Arguments

Dr. Stone's argument rests on several different pieces of evidence:

-Clinical trials data on transaminase elevations:

-Dr. Stone argues that the transaminase signal is dose dependent and gets stronger as the threshold for abnormality increases, and is associated with clinical symptoms in many cases. He particularly focuses on 30 cases with increases to greater than 10 times ULN. Although he suggests that 2 of these cases met Hy's Law criteria, he acknowledges that, in both cases, there are plausible alternative explanations. Dr. Crentsil disputes the 2 purported Hy's Law cases, for the reasons that Dr. Stone himself acknowledges as problematic.

Comment: As Dr. Crentsil notes, we have known about the transaminase signal from the beginning, and this by itself is not an argument for a box warning.

-Lilly's retrospective cohort study (i3 Aperio):

-This study was extensively discussed at the 1-22-10 meeting with Lilly. Dr. Stone conducted his own analysis of the data from this study, focusing on the first 90 days of exposure and pooling the data across all comparator drugs. Lilly strongly objected to Dr. Stone's methods of analysis, and also argued that the study was flawed because it was not limited to serious liver injury cases and the propensity matching failed to address the confounding. Dr. Crentsil agrees with Lilly that the study was fatally flawed and cannot be relied upon to assess relative risk of liver injury for these drugs.

Comment: Lilly is planning an expanded cohort study, and we have provided comments on the protocol (4-29-10 letter). I am not persuaded that the study results provided to date are interpretable as evidence for duloxetines's greater potential for serious liver injury compared to other antidepressants.

-Excess AERS reports of liver injury with duloxetine:

-Dr. Stone argues that the reporting rate for AERS liver injury cases is 3-8 times higher for duloxetine compared to other antidepressants. Lilly argues that the cases are predominantly not serious liver injury cases, and that there is confounding by indication. Dr. Stone disputes the confounding. Dr. Crentsil agrees with Lilly that, without limiting

the analysis to confirmed serious liver injury cases, the analyses are of little value with regard to the question of a box warning for duloxetine.

Comment: I agree that this type of analysis does not provide persuasive evidence in support of a box warning.

-FDA's blinded review of liver injury for 3 antidepressants:

-This was an academic exercise conducted to see if, qualitatively, liver injury cases for duloxetine were more like paroxetine cases or nefazodone cases in terms of subjective assessment of probable causal relatedness to drug. Again, the major flaw is that the cases were not limited to the most serious cases (liver failure leading to death or transplant).

Comment: This analysis does not really contribute much, in my view, to answering the question of whether or not duloxetine should have a box warning.

-Disproportionality analysis for liver injury cases for antidepressants:

-Dr. Stone argues that the data-mining scores for duloxetine are more comparable to those for nefazodone than for other antidepressants. Again, the problem is that most of the cases included are not the most serious events we care most about.

Comment: The sponsor argued that the only outcome that was particularly relevant was hepatic failure, for which duloxetine and paroxetine looked identical, and very different compared to nefazodone.

-Case reports duloxetine liver injury:

-What this discussion essentially comes down to is whether or not there are unconfounded cases of death or transplant due to hepatic failure in association with duloxetine exposure. Dr. Stone focuses on one case (the Hanje et al report). Dr. Crentsil argues against this as a clean case.

Comment: I think the most serious obstacle to concluding that duloxetine deserves a box warning is the inability to find even a single clean case of death or transplant due to hepatic failure, despite over 7 million person years of exposure (about 25 million total patients exposed).

Dr. Stone's argument that duloxetine and nefazodone share sufficient similarities to justify a box warning for duloxetine:

-As summarized above, Dr. Stone in several of his analyses has tried to make a case that duloxetine looks more like nefazodone than other antidepressants with regard to hepatotoxicity. Dr. Crentsil has argued that most of these analyses are problematic because they are not limited to the most serious hepatic injury cases we care about. With regard to the most serious cases, there seems to be agreement that there are no "clean" cases for duloxetine, while there are at least 2 for nefazodone, probably more, with only about 1/5 of the use compared to duloxetine.

Comment: Dr. Crentsil has argued, and I agree, that an independent case for duloxetine as a serious hepatotoxin needs to be made to support adding a box warning for duloxetine. This has not been done, in my view. Regarding a similarity to nefazodone, not only has a sufficient case for the similarity not been made, but basing an argument largely on such a comparison is not sufficient, in my view.

Conclusion

This has been an evolving process over the last 6 years, and I think we have established that duloxetine is capable of causing substantial transaminase elevation, associated in some cases with clinical symptoms. I also agree with the view that this is a drug that bears continued close surveillance regarding hepatotoxicity. I agree, however, with Dr. Crentsil that a sufficient case has not been made to justify adding a box warning regarding hepatotoxicity for duloxetine. Duloxetine already has, as I have noted, very strong labeling regarding hepatic injury, and I think that labeling remains adequate, given the current level of evidence for hepatic injury. Although there is an impressive amount of evidence pointing to hepatic injury for duloxetine, the most important missing piece to support a box warning and second line status is the absence of clean cases of death or transplant due to hepatic failure. Given this doubt, I am reluctant to ask for a box warning for this drug. The only rationale for a box warning would be that we had reached a conclusion that this drug should not be used as a first line treatment for its approved indications. I do not believe we have reached that point.

An advisory committee is planned for duloxetine in August, 2010, to discuss the NDA for chronic pain. It is likely that the hepatotoxicity issue will be on the agenda for this meeting, and this will be another opportunity to discuss the current level of evidence. One useful outcome of having this public meeting is that, for the first time, we will be able to share all of our documents with Lilly. They have complained over the years that they have not had full access to our review documents, and therefore, have not been able to fully understand and replicate our results. With full disclosure of all of our review documents, they will have that opportunity.

cc:

Orig IND/NDA

HFD-130/DivFile

HFD-130/TLaughren/MMathis/VCrencsil/MStone

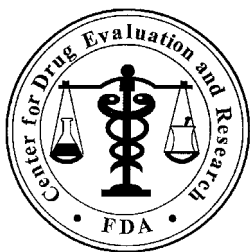
DOC: Dulox Memo.doc

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21427	ORIG-1	ELI LILLY AND CO	CYMBALTA(DULOXETINE HCL)20,30,40,60MG

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/s/

THOMAS P LAUGHREN
05/18/2010



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: July 19, 2010

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Subject: Updated Safety Profile

Drug Name(s): Duloxetine

Application Type/Number: NDA 21427, NDA 21733, NDA 22148

Applicant/sponsor: Eli Lilly

OSE RCM #: 2010-1208

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EXECUTIVE SUMMARY

In preparation for an upcoming Advisory Committee (AC) meeting, the Division of Anesthesia and Analgesia Products (DAAP) requested that the Division of Pharmacovigilance (DPV) provide a summary document of the safety profile for duloxetine. This review incorporates safety data from both the premarketing and postmarketing phases of drug development. The information gathered from a New Molecular Entity (NME) Postmarketing Safety Evaluation conducted on 13 March 2007 was consistent with the recent FDAAA requirement for FDA to review the safety profiles of all new drugs¹. This was a collaborative effort, primarily conducted by two offices within FDA, to assess safety concerns listed in the product labeling and postmarketing information gathered from spontaneous reports, epidemiological data, and literature findings.

OSE determined that most of the postmarketing safety findings were reflected in the product label. A few findings led OSE to perform thorough analyses of AERS cases of urinary retention/hesitation, bleeding disorders, Steven-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN), and serious liver injury. Each of these new safety reviews led to subsequent modifications to the duloxetine label, with the exception of TEN.

At the time of the NME evaluation in 2007, DPV provided the top 50 adverse event preferred terms (PT) reported with duloxetine from the approval date in 2004 through 28 February 2007. At that time, the only terms identified as unlabeled events were “fall”, “dyspnoea”, and “chest pain”. For the purpose of this update, we repeated a search in the AERS database to retrieve the top 50 adverse events reported with duloxetine since the NME evaluation, date of output 28 February 2007, through 11 June 2010. Since 2007, many of the updated adverse event terms were found to be a duplication of the terms found in the NME evaluation. In our updated search, the term “chest pain” was not one the top PTs reported, as it was in the NME evaluation. In contrast, the terms “fall” and “dyspnoea” have continued to be reported in AERS as two of the top 50 PTs. The risk of falls is currently reflected in the duloxetine label. The reported event “dyspnoea” has not been considered as a potential safety signal at this time.

DPV recommends that the duloxetine safety profile reflected in the current product label be considered as part of an overall assessment of the benefit-risk of this product for the newly proposed indication of chronic pain.

1 INTRODUCTION

In preparation for an upcoming AC meeting, DAAP requested that DPV provide a summary document of the safety profile for duloxetine. This review provides an update of safety information since the NME Postmarketing Evaluation was performed on 13 March 2007.¹

1.1 REGULATORY HISTORY

Cymbalta® (duloxetine hydrochloride) is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) for oral administration. Although the exact mechanisms of the antidepressant, central pain inhibitory and anxiolytic actions of duloxetine in humans are unknown, these actions are believed to be related to its potentiation of serotonergic and noradrenergic activity in the central nervous system (CNS).²

Table 1. Summary of the approved indications for duloxetine

Indication	Approval Date
Major Depressive Disorder (MDD)	August 3, 2004
Generalized Anxiety Disorder (GAD)	November 19, 2009
Diabetic Peripheral Neuropathic Pain (DPNP)	September 3, 2004
Fibromyalgia (FM)	June 13, 2008

1.2 IMPORTANT SAFETY EFFECTS OF DULOXETINE CAPTURED IN THE CURRENT PRODUCT LABELING

*Safety Effects Captured in the CONTRAINDICATIONS Section:*²

- Use of a monoamine oxidase inhibitor concomitantly or in close temporal proximity
- Use in patients with uncontrolled narrow-angle glaucoma

*Safety Effects Captured in the WARNINGS AND PRECAUTIONS Section:*²

- Suicidality: Monitor for clinical worsening and suicide risk
- Hepatotoxicity: Hepatic failure, sometimes fatal, has been reported in patients treated with Cymbalta. Cymbalta should be discontinued in patients who develop jaundice or other evidence of clinically significant liver dysfunction and should not be resumed unless another cause can be established. Cymbalta should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease
- Orthostatic Hypotension and Syncope: Cases have been reported with duloxetine therapy.
- Serotonin Syndrome, or Neuroleptic Malignant Syndrome (NMS)-like reactions: Serotonin syndrome or NMS-like reactions have been reported with SSRIs and SNRIs. Discontinue Cymbalta and initiate supportive treatment.
- Abnormal Bleeding: Cymbalta may increase the risk of bleeding events. Patients should be cautioned about the risk of bleeding associated with the concomitant use of duloxetine and NSAIDs, aspirin, or other drugs that affect coagulation.
- Discontinuation: May result in symptoms, including dizziness, nausea, headache, fatigue, paresthesia, vomiting, irritability, nightmares, insomnia, diarrhea, anxiety, hyperhidrosis, and vertigo
- Activation of mania or hypomania has occurred
- Seizures: Prescribe with care in patients with a history of seizure disorder

- Blood Pressure: Monitor blood pressure prior to initiating treatment and periodically throughout treatment
- Inhibitors of CYP1A2 or Thioridazine: Should not administer with Cymbalta
- Hyponatremia: Cases of hyponatremia have been reported
- Hepatic Insufficiency and Severe Renal Impairment: Should ordinarily not be administered to these patients
- Controlled Narrow-Angle Glaucoma: Use cautiously in these patients
- Glucose Control in Diabetes: In diabetic peripheral neuropathic pain patients, small increases in fasting blood glucose, HbA1c, and total cholesterol have been observed
- Conditions that Slow Gastric Emptying: Use cautiously in these patients
- Urinary Hesitation and Retention

Safety Effects Captured in the ADVERSE REACTIONS Section:²

- Most common adverse reactions ($\geq 5\%$ and at least twice the incidence of placebo patients): nausea, dry mouth, constipation, somnolence, hyperhidrosis, and decreased appetite

Safety Effects Captured in the DRUG INTERACTIONS Section:²

- Potent inhibitors of CYP1A2 should be avoided
- Potent inhibitors of CYP2D6 may increase duloxetine concentrations
- Duloxetine is a moderate inhibitor of CYP2D6

1.3 PREVIOUS DPV REVIEWS

On 13 March 2007 reviewers from the Office of Surveillance and Epidemiology (OSE) and the Office of Drug Evaluation I (ODE I) within FDA's Center for Drug Evaluation and Research (CDER) presented an overview of their safety data for duloxetine as part of the New Molecular Entity (NME) Postmarketing Safety Evaluation Pilot Program. The evaluation was a systematic, collaborative process which involved a review of potential safety concerns identified for duloxetine since its approval by the FDA. Data presented during this meeting included information on adverse events in the Adverse Event Reporting System (AERS) database, a data mining analysis of AERS data, a literature review, a medication error analysis, and a discussion of postmarketing clinical trial findings. The surveillance procedure identified some previously unrecognized safety issues and provided more information about some previously known safety issues for duloxetine³. New safety signals requiring further investigation and analysis were thoroughly discussed between the two offices.¹ Findings of the NME evaluation that were considered necessary for further review are summarized in section 1.3.1, 1.3.2, and 1.3.3 below, as well as thorough safety reviews completed by OSE since the completion of the evaluation. These evaluations are included in the background material provided with this document.

1.3.1 New Molecular Entity (NME) Postmarketing Evaluation

On 8 May 2007 the Duloxetine NME Review team completed a postmarketing safety screening evaluation of duloxetine to identify safety issues that were considered necessary for further review.³ The major findings of this evaluation spanned multiple postmarketing data streams. Five potential new safety signals prompted further assessment; blindness, falls/loss of consciousness, bleeding disorders, urinary hesitancy, and drug interactions. A plan to perform a series of thorough reviews for these events, utilizing the AERS database, was undertaken.

As a result of the evaluation, the following action items were carried out:

The AERS cases of “blindness” were deemed to be unrelated to the use of duloxetine; however, the adverse event appeared to instead, be related to the underlying disease or other causes. It was also felt that the “risk of falls” was appropriately reflected in the current labeling and that “loss of consciousness” is an event associated with multiple possible causes that are currently listed in labeling, thus further review of these events were not undertaken.

A signal of “drug interactions” was considered for further review by DPV, although no continued action was taken since it was determined that many of the drug interactions were explained by the drug information provided in the duloxetine label. In addition, DPV identified reports describing a potential interaction between duloxetine and warfarin and determined that the interaction was appropriately labeled in the “Drug Interaction” section of the duloxetine label.

In contrast, AERS signals of “urinary retention/hesitancy” and “bleeding disorders” were fully reviewed by DPV through analysis of case series developed for each of these events. A summary of the review findings can be found in sections 1.3.2 and 1.3.3. In 2008, OSE also performed full AERS reviews of “SJS/TEN” and “serious liver injury”, which are summarized in sections 1.3.4 and 1.3.5.

1.3.2 Urinary Retention/Hesitation

DPV completed a full safety review dated 11 July 2007, which evaluated postmarketing reports of urinary retention and urinary hesitation associated with duloxetine.⁴

OSE recommended adding “urinary retention that resulted in hospitalization and, or catheterization as seen in postmarketing cases” to the Precautions section of duloxetine label.

Prior to this review, labeling about urinary retention or hesitation was included in the “Adverse Reaction” section of duloxetine. In the November 2007 label revision, information about urinary retention requiring hospitalization and/or catheterization associated with duloxetine use was added to the “Postmarketing” section.

1.3.3 Bleeding

DPV completed a full safety review on 18 September 2007, which evaluated postmarketing reports of bleeding events with duloxetine.⁵

DPV recommended the following:

- Adding the “Abnormal Bleeding” statement in the “Precaution” section of the SSRI labels to the duloxetine label
 - “SSRIs and SNRIs may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anticoagulants may add to the risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.”⁶
- Adding the drug interaction language for warfarin and drugs that affect hemostasis (ASA, NSAIDs, and anticoagulants) found in the SSRI labels to the duloxetine label

- Adding patient information language regarding concomitant use of ASA, NSAIDs, or anticoagulants found in the SSRI labels to the duloxetine label.

Prior to this review, labeling about the risk of bleeding was not included in the label for duloxetine. In the November 2007 label revision, all DPV proposed label changes to reflect the risk of bleeding with duloxetine were added to the “Warnings and Precautions”, “Drug Interactions”, and “Patient Counseling Information” sections.

1.3.4 SJS, TEN

DPV completed a full safety review on 6 August 2008, which evaluated postmarketing reports of serious skin disorders SJS and TEN among the SSRIs and SNRIs and compared the reporting rates across products.⁷

OSE recommended elevating the current serious skin labeling to the “Warnings and Precautions” section and adding language about the fatality potential with SJS/TEN to the “Postmarketing” section of the duloxetine label.

Prior to this review, the labeling for serious skin reactions for duloxetine stated “serious skin reactions including Stevens-Johnson Syndrome that have required drug discontinuation and/or hospitalization have been reported with duloxetine”, and to date, no current labeling changes have been made as a result of this review.

1.3.5 Serious Liver Injury

In addition to the previous OSE reviews regarding the potential liver toxicity for duloxetine, DPV completed a full review on 20 August 2008, which evaluated postmarketing reports of serious liver injury associated with the SNRIs duloxetine, desvenlafaxine, and venlafaxine.⁸

The review stated that hepatotoxicity associated with duloxetine therapy was recognized and labeled in the “Warning and Precautions” section.

DPV recommended that the “sponsor use 15-day reporting of all elevated transaminase levels with elevated bilirubin levels, clinical jaundice or any suggestion of serious liver injury; sponsor monitor for liver toxicity and actively pursue follow-up for any reports of elevated transaminase levels with elevated bilirubin levels, clinical jaundice or any indication of serious liver injury; and add labeling in the “Information for Patients” section and the Medication Guide to instruct patients to discontinue duloxetine and contact their primary care physician if they experience dark urine or a yellow discoloration of the eyes, inside the mouth, or skin.”

At that time, DPP felt that the potential for liver toxicity was appropriately reflected in the current labeling.

2 METHODS AND MATERIALS

2.1 AERS DATABASE

We conducted a thorough search in the AERS database to retrieve all adverse event reports associated with duloxetine from 28 February 2007 to 11 June 2010. Drug terms we searched were duloxetine and Cymbalta®.

3 RESULTS

3.1 ADVERSE EVENTS CASES

Table 1 provides a list of the top 50 MedDRA preferred terms from the AERS database since the NME Postmarketing Evaluation, from 28 February 2007 to 11 June 2010. The following adverse events are sorted by decreasing number.

Table 1. AERS Crude Counts of the Top 50 Preferred Term Adverse Events from 28 February 2007 to 11 June 2010

Key: BB=Black Box Warning DA=Dosage and Administration WP=Warnings and Precautions AR=Adverse Reactions CI=Contraindications
MG=Medication Guide SP=Use in Specific Populations PCI=Patient Counseling Information OD=Overdose BP=Blood Pressure

Rank	Preferred Term	Count of PTs	% of Total	Label Status	Label Location	Term(s) Used In Label	Comments
1	Nausea	685	9.85	Labeled	AR, WP		
2	Dizziness	643	9.25	Labeled	WP,A/R,PCI		
3	Headache	457	6.57	Labeled	WP, AR		
4	Drug Withdrawal Syndrome	442	6.36	Labeled	DA,WP,SP	Discontinuation, discontinuation syndrome	
5	Feeling Abnormal	371	5.34	Labeled	AR		
6	Paraesthesia	369	5.31	Labeled	AR		
7	Insomnia	363	5.22	Labeled	WP,AR,PCI,MG		
8	Fatigue	354	5.09	Labeled	WP,AR		
9	Depression	328	4.72	Labeled	WP,PCI,MG		
10	Suicidal Ideation	318	4.57	Labeled	BB,WP, AR,MG, PCI	Suicidal ideation, suicidal thinking, suicidality, suicide risk	
11	Vomiting	303	4.36	Labeled	WP,OD, AR, SP		
12	Anxiety	293	4.22	Labeled	AR,WP, PCI,MG		
13	Alanine Aminotransferase Increased	287	4.13	Labeled	WP	Elevation of transaminase levels, ALT elevation	

Rank	Preferred Term	Count of PTs	% of Total	Label Status	Label Location	Term(s) Used In Label	Comments
14	Completed Suicide	286	4.11	Labeled	AR		
15	Hyperhidrosis	277	3.99	Labeled	WP,AR		
16	Hepatic Enzyme Increased	274	3.94	Labeled	WP	Elevation of transaminase levels, ALT and AST elevation	
17	Drug Ineffective	272	3.91	-----			
18	Drug Interaction	272	3.91	Labeled	DI		Label contains “Drug Interaction” section which includes information about CYP1A2 and CYP2D6 being responsible for duloxetine metabolism.
19	Tremor	265	3.81	Labeled	AR,SP		
20	Pain	254	3.65	Labeled	AR	Abdominal pain, ear pain, pharyngolaryngeal pain, musculoskeletal pain	
21	Aspartate Aminotransferase Increased	243	3.5	Labeled	WP	Elevation of transaminase levels, AST elevation	
22	Malaise	235	3.38	Labeled	AR		
23	Diarrhoea	232	3.34	Labeled	WP, AR		
24	Fall	232	3.34	Labeled	WP,AR, OD, PCI	Falls, somnolence, sedation and dizziness	Associated with hyponatremia; somnolence, sedation and dizziness may lead to falls.
25	Somnolence	225	3.24	Labeled	AR, OD		
26	Loss Of Consciousness	223	3.21	Labeled	WP, OD, CI	Coma	Associated with hyponatremia; in overdose situations; concomitant use with MAOIs; serotonin syndrome
27	Weight Increased	202	2.91	Labeled	AR		

Rank	Preferred Term	Count of PTs	% of Total	Label Status	Label Location	Term(s) Used In Label	Comments
28	Suicide Attempt	192	2.76	Labeled	BB,AR,WP	Suicide attempt, suicidality	
29	Crying	178	2.56	Labeled	SP	Constant crying	Labeled for infants, also can be associated with the underlying disease of depression, for which duloxetine is indicated as treatment
30	Blood Pressure Increased	176	2.53	Labeled	WP,AR,OD	Hypertension, ↑ in mean BP, mean ↑ in systolic BP, mean ↑ in diastolic BP, ↑ in supine BP	
31	Confusional State	173	2.49	Labeled	WP,AR	Confusional state, confusion	
32	Hypertension	166	2.39	Labeled	WP,AR,OD	Hypertension, ↑ in mean BP, mean ↑ in systolic BP, mean ↑ in diastolic BP, ↑ in supine BP	
33	Irritability	165	2.37	Labeled	WP, AR, SP, PC		
34	Withdrawal Syndrome	163	2.34	Labeled	DA,WP, SP	Discontinuation, discontinuation syndrome	
35	Asthenia	161	2.32	Labeled	AR		
36	Decreased Appetite	159	2.29	Labeled	AR		
37	Drug Exposure During Pregnancy	157	2.26	Labeled	SP		Label states the risks associated with neonates exposed to duloxetine during third trimester of pregnancy; discusses weighing risk versus benefit to justify using duloxetine during pregnancy.

Rank	Preferred Term	Count of PTs	% of Total	Label Status	Label Location	Term(s) Used In Label	Comments
38	Liver Function Test Abnormal	153	2.2	Labeled	WP	Elevation of transaminase levels, liver transaminase elevations	
39	Agitation	152	2.19	Labeled	CI,WP,AR,PCI		
40	Convulsion	152	2.19	Labeled	WP, AR, SP, OD	Seizures, convulsions	
41	Death	146	2.1	Labeled	WP	Sudden death, Death	Sudden death associated with concomitant use with thioridazine; death associated with hyponatremia
42	Disturbance In Attention	144	2.07	Labeled	AR		
43	<i>Dyspnoea</i>	143	2.06	<i>Not Labeled</i>			
44	Anger	139	2	Labeled	AR		
45	Vision Blurred	139	2	Labeled	AR		
46	Hospitalisation	135	1.94	Labeled	WP,AR,SP		Associated with urinary retention; complications in neonate when drug used in third trimester of pregnancy
47	Nightmare	135	1.94	Labeled	WP,AR		
48	Weight Decreased	130	1.87	Labeled	AR	Weight changes, weight decreased	
49	Palpitations	129	1.86	Labeled	AR		
50	Abnormal Behaviour	128	1.84	Labeled	BB,WP,PCI	Unusual changes in behavior, suicidal thinking and behavior	

4 DISCUSSION

Duloxetine's safety issues have been extensively reviewed by both OND and OSE reviewers, as recognized by the NME Postmarketing Evaluation dated 13 March 2007¹. Since that time, potential safety issues were reviewed by OSE, which included urinary retention/hesitation, bleeding disorders, Steven-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN), and serious liver injury. The current labeling of duloxetine now reflects the risks for urinary hesitation and retention (warnings and precautions), bleeding abnormalities (warnings and precautions), SJS requiring hospitalization (postmarketing section), and liver toxicity (warnings and precautions).

For the purpose of this review, we provide an update of the top 50 adverse event terms reported for duloxetine since the NME evaluation in 2007. Many of the updated adverse event terms are found to be a duplication of the terms found in the NME evaluation. Our primary focus was to compare previously unlabeled adverse events identified in the NME evaluation with unlabeled adverse events reported in AERS. In our updated search, the term "chest pain" was not one of the top PTs reported, as it was in the NME evaluation. In contrast, the terms "fall" and "dyspnoea" have continued to be reported in AERS as two of the top 50 PTs. The risk of falls is currently reflected in the duloxetine label. The reported event "dyspnoea" has not been considered as a potential safety signal at this time.

5 CONCLUSION

There are a series of known safety effects of duloxetine enunciated in the product label. Recently, the risk of urinary retention/hesitation, bleeding, SJS, serious liver injury, , and falls/loss of consciousness have been added. The current product label appears to reflect our current understanding of the safety profile of duloxetine.

6 RECOMMENDATIONS

DPV recommends that the duloxetine safety profile reflected in the product label be considered as part of an overall assessment of the benefit-risk of this product for the newly proposed indication of chronic pain.

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8. Lyndly J et al. FDA Post-marketing safety review: Serious Liver Injury (SLI), 20 August 2008.

8 APPENDICES

8.1 APPENDIX A. NME POSTMARKETING EVALUATION OF AERS CRUDE COUNTS OF THE TOP 50 ADVERSE EVENTS FROM APPROVAL TO 28 FEBRUARY 2007

Rank	Preferred Term	Count of PTs	Percent of Total	Label Status
1	Nausea	724	11.16	Labeled
2	Feeling Abnormal	509	7.84	Labeled
3	Dizziness	482	7.43	Labeled
4	Insomnia	392	6.04	Labeled
5	Fatigue	368	5.67	Labeled
6	Headache	348	5.36	Labeled
7	Blood Pressure Increased	312	4.81	Labeled
8	Somnolence	310	4.78	Labeled
9	Depression	300	4.62	Labeled
10	Drug Ineffective	282	4.35	-----
11	Anxiety	262	4.04	Labeled
12	Hyperhidrosis	261	4.02	Labeled
13	Tremor	253	3.90	Labeled
14	Vomiting	237	3.65	Labeled
15	Diarrhoea	220	3.39	Labeled
16	Alanine Aminotransferase Increased	209	3.22	Labeled
17	Agitation	203	3.13	Labeled
18	Suicidal Ideation	200	3.08	Labeled
19	Aspartate Aminotransferase Increased	180	2.77	Labeled
20	Fall	180	2.77	Not Labeled
21	Asthenia	175	2.70	Labeled
22	Hepatic Enzyme Increased	167	2.57	Labeled
23	Loss of Consciousness	166	2.56	Labeled
24	Convulsion	160	2.47	Labeled
25	Malaise	158	2.43	Labeled
26	Constipation	155	2.39	Labeled
27	Paraesthesia	154	2.37	Labeled
28	Hypertension	152	2.34	Labeled
29	Confusional State	149	2.30	Labeled
30	Pain	147	2.27	Labeled
31	Drug Interaction*	140	2.16	-----
32	Dry Mouth	138	2.13	Labeled
33	Drug Withdrawal Syndrome	129	1.99	Labeled
34	Dyspnoea	123	1.90	Not Labeled
35	Crying	120	1.85	Labeled for infants
36	Weight Increased	118	1.82	Labeled
37	Irritability	117	1.80	Labeled
38	Vision Blurred	116	1.79	Labeled
39	Heart Rate Increased	115	1.77	Labeled
40	Prescribed Overdose	115	1.77	-----
41	Suicide Attempt	112	1.73	Labeled
42	Anorexia	108	1.66	Labeled
43	Chest Pain	108	1.66	Not Labeled
44	Nervousness	104	1.60	Labeled
45	Hallucination	99	1.53	Labeled
46	Abdominal Pain Upper	95	1.46	Labeled
47	Completed Suicide	86	1.33	Labeled
48	Condition Aggravated	86	1.33	Labeled
49	Pruritis	85	1.31	Labeled
50	Weight Decreased	85	1.31	Labeled

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21427	ORIG-1	ELI LILLY AND CO	CYMBALTA(DULOXETINE HCL)20,30,40,60MG
NDA-21733	ORIG-1	ELI LILLY AND CO	CYMBALTA (DULOXETINE HYDROCHLORIDE)20/30
NDA-22148	ORIG-1	ELI LILLY AND CO	CYMBALTA
NDA-22516	ORIG-1	ELI LILLY AND CO	CYMBALTA

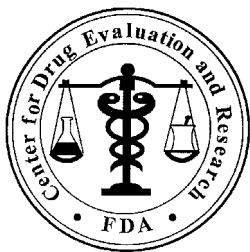
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/s/

LAURELLE CASCIO
07/19/2010

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MARK I AVIGAN
07/19/2010



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: August 20, 2008

To: **Division of Psychiatric Products (DPP)**
Thomas Laughren, MD, Director

From: **Office of Surveillance and Epidemiology (OSE)**

DVPI **Division of Pharmacovigilance I**
Thru: Mark Avigan, MD, CM, Director
From: Jenna Lyndly, R.N., Safety Evaluator

DEPI **Division of Epidemiology (DEPI)**
Thru: Solomon Iyasu, MD, MPH, Director
From: Cynthia Kornegay, Ph.D., Epidemiologist and
Hina Mehta, PharmD, Drug Utilization Data Analyst

Subject: Serious Liver Injury (SLI)

Drug Name(s): Cymbalta® (duloxetine), Effexor®, Effexor XR®
(venlafaxine), Pristiq® (desvenlafaxine)

Application Type & Number: desvenlafaxine – NDA 21-992, duloxetine - NDA 21-733 &
NDA 21-427, venlafaxine - NDA 20-151 & NDA 20-699

Applicant/sponsor: Lilly – duloxetine, Wyeth - desvenlafaxine & venlafaxine

OSE RCM #: 2006-410

Acknowledgement: John R. Senior, M.D., Associate Director for Science, Office of Surveillance and Epidemiology (OSE)

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EXECUTIVE SUMMARY

OSE, in response to a consultation request from DPP¹, identified 26 postmarketing cases of serious liver injury that appear to be associated with venlafaxine therapy, 21 from AERS, and 5 from the medical literature. Venlafaxine's association with serious liver injury prompted four of the five authors of published cases to recommend monitoring of liver functions, particularly for patients with pre-existing liver disease. In addition, two of the articles note that clinicians should be aware of and consider venlafaxine's association with serious liver injury in patients on venlafaxine therapy who become symptomatic.

In addition, OSE reviewed serious liver injury for the remaining two serotonin and norepinephrine reuptake inhibitors (SNRIs), desvenlafaxine, and duloxetine. Desvenlafaxine clinical trials include reports of elevated liver enzymes including a case that met the criteria for Hy's Law.^{2,3,4,5} Duloxetine's association with serious liver injury is recognized and labeled in the Warning and Precautions section.⁶

Based on a review of the animal studies, the clinical trial data, and adverse events from the medical literature and AERS, the three SNRIs, venlafaxine, desvenlafaxine, and duloxetine, appear to be linked to a risk for clinically serious idiosyncratic hepatotoxicity. The current labeling for venlafaxine and desvenlafaxine does not appear sufficient to alert health care providers of the potential for serious liver injury. Labeling should be modified for both drugs to convey the 'possible'⁷ risk for serious liver injury. In addition, early notification of potential cases of serious injury with SNRI therapy will allow the FDA to efficiently monitor the potential public health risk and respond in a timely manner.

Therefore, OSE recommends the following:

1. Request that the SNRI sponsors to use 15-day reporting of all elevated transaminase levels with elevated bilirubin levels, clinical jaundice or serious liver injury e.g., hepatitis, liver failure, hepatic necrosis
2. Request that the SNRI sponsors to monitor for liver toxicity and actively pursue follow-up for any reports of elevated transaminase levels with elevated bilirubin levels, clinical jaundice or serious liver injury e.g., hepatitis, liver failure, hepatic necrosis
3. Add labeling to the Warning and Precautions section for venlafaxine and desvenlafaxine indicating the 'possible' risk of serious liver injury.
4. Add labeling in the Information for Patients section and the Medication Guide to instruct patients to discontinue the SNRI and contact their primary care physician if they experience dark urine or a yellow discoloration of the eyes, inside of the mouth, or skin.

¹ The capacity of a drug, chemical, or other exposure to produce injury to the liver, "Lippincott Williams & Wilkins, 2006, Stedman's Medical Dictionary, -28th ED, hepatotoxicity
² FDA, 2007, Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) Drug-Induced Liver Injury: Premarketing Clinical Evaluation, Draft Guidance for Industry, October 2007.

³ Raheja, K. NDA 021966, Pharmacology/Toxicology Review and Evaluation, 06/23/06

⁴ Levin, R. NDA 021992, Clinical Review, 10/24/06

⁵ Senior, J. OSE Memorandum, Possible hepatotoxicity of desvenlafaxine (PRISTIQ, Wyeth), 03/28/07

⁶ Cymbalta, NDA 021427, label approved on 11/28/07

⁷ See Appendix 8 6, The Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring, Practical Pharmacovigilance, Causality Assessment of Suspected Adverse Reactions

1 BACKGROUND

1.1 INTRODUCTION

OSE reviewed venlafaxine hepatotoxicity in response to a consultation request from DPP, as DPP had identified published cases of venlafaxine hepatotoxicity (Dubitsky 2006). OSE was asked to provide a case review, reporting rates and a literature search for case report of venlafaxine hepatotoxicity. In addition, OSE reviewed the hepatotoxicity of duloxetine and desvenlafaxine, which are also classified as SNRIs.

1.2 SNRI REGULATORY HISTORY

On December 28, 1993, Effexor® (venlafaxine) was approved for the treatment of a major depressive disorder (MDD). Effexor XR® was approved October 20, 1997 for the treatment of generalized anxiety disorder (GAD), major depressive disorder (MDD), panic disorder, and social anxiety disorder.

On August 3, 2004, Cymbalta® (duloxetine) was approved for the indications of MDD, GAD, and diabetic peripheral neuropathic pain (DPNP).

On February 28, 2008, Pristiq® (desvenlafaxine) was approved to treat MDD.

In June 2006, Pristiq® was submitted for the indication of moderate to severe vasomotor symptoms associated with menopause. On April 23, 2007, the Division of Reproductive and Urologic Products, (DRUP) recommended a nonapprovable action based on a lack of substantial evidence of efficacy and insufficient information to determine if Pristiq was safe for use under the conditions suggested in the proposed labeling (Furlong 04/10/07). The Division recommended a blinded, randomized, placebo-controlled Phase III study of one year duration to address the safety issues. The major safety issues identified by DRUP were cardiac ischemia and liver toxicity (Furlong 05/18/07).

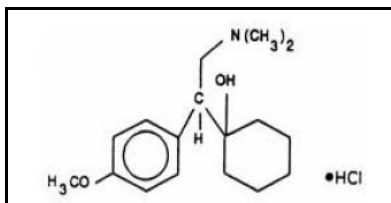
1.3 SNRI PHARMACOKINETICS

Venlafaxine, duloxetine, and desvenlafaxine are the three drugs currently classified as SNRIs. As with other antidepressants, the method of action for the SNRIs is not known but is purportedly related to neurotransmitter activity in the central nervous system. The active metabolite of venlafaxine is O-desmethylenlafaxine (ODV). Desvenlafaxine is the succinate salt of ODV. The characteristic of the three SNRIs are compared below.

Table 1. Metabolism and Binding Characteristics of SNRIs

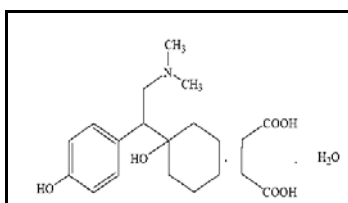
	Duloxetine	Venlafaxine	Desvenlafaxine
Metabolism	CYP1A2 and CYP2D6	CYP2D6	CYP3A4
Inhibitor	CYP1A2 - yes CYP2D6 - mod CYP3A4 - no	CYP2D6 – weak CYP3A4 – no CYP1A2 - no	CYP3A4 - no CYP2D6 – weak CYP1A2 - no
Norepinephrine	Ki 7.5nM	Ki 2480nM	Ki 558.4nM
Serotonin	Ki 0.8nM	Ki 82nM	Ki 40.2nM
Dopamine	Ki 240nM	Ki 7647nM	Weak
Protein Binding	>90%	Not highly bound	Not highly bound
Hepatic Insufficiency	mod Child-Pugh B 5-fold increase in AUC, half-life prolonged X 3 mean plasma clearance decreased by 85%	cirrhosis venlafaxine half-life prolonged by 30%, clearance decreased by 50% ODV half-life prolonged by 60%, clearance decreased by 30% severe cirrhosis venlafaxine clearance decreased ~90%	mod Child-Pugh B 31% increase in AUC, clearance decreased by 20% severe Child-Pugh C 35% increase in AUC clearance decreased by 36%
Dose	Don't administer to patients with any hepatic insufficiency	Decrease dose by 50% in patients with mild-mod impairment	No decrease in dose do not exceed 100 mg/day (recommended dose for all patients 50 mg/day)

(Bymaster 2001, Clark et al 2007, Cymbalta 11/28/07, Deecher et al 2006, Pristiq 02/28/08)



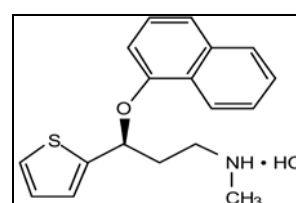
venlafaxine (Effexor 02/11/2008)

C₁₇H₂₇NO₂ HCl



desvenlafaxine (Pristiq 02/28/2008)

C₁₆H₂₅NO₂ (free base) and
C₁₆H₂₅NO₂•C₄H₆O₄•H₂O
(succinate
monohydrate)



duloxetine (Cymbalta 11/28/2007)

C₁₈H₁₉NOS•HCl

Effects on liver morphology were seen in the animal studies with venlafaxine, desvenlafaxine, and duloxetine; however, Martignoni, Groothuis, and Kanter 2006 noted that caution should be used when extrapolating metabolism data from animal models to humans for CYP1A, 2D and 3A isoenzymes as interspecies differences are a “major cause” of species differences in drug metabolism.

Venlafaxine’s liver effects were seen in the animal studies with rats, dogs and monkeys. In the one month venlafaxine rat study, a dose related increase in alkaline phosphatase (ALP) (10-60%) was noted at doses of 75-675 mg/kg/day.

In the one month venlafaxine dog study, one of three dogs experienced a 2.5 fold increase in ALP at weeks 2 and 4 at a 15/mg/kg/day dose. In addition, liver weights were increased by 11-29% at 75-175/mg/kg/day doses. At week six, in the three month study, two of three male dogs experienced a two to five fold increase in alanine transaminase (ALT), aspartate aminotransferase (AST), and ALP at a 100 mg/kg/day dose. Similar effects were seen in two of three female dogs, at weeks six and thirteen, at a dose of 300mg/kg/day. Dose related increases of 7-27% in liver weight were seen at 100-300 mg/kg/day doses.

At week 1, male Rhesus monkeys dosed with 80mg/kg/day of venlafaxine and females with 125mg/kg/day of venlafaxine, experienced eight to ten fold increases in ALT and three to six fold increases in AST, consistent with ‘possible’ hepatocellular injury; however the levels returned to normal at week 4 (Sparenborg 04/16/93).

In the animal studies for desvenlafaxine, NDA 021966, increases in liver enzymes in dogs was seen at high doses, but histopathologic liver changes were not seen. In the 1-week study, one of two female dogs receiving 400mg/kg/day experienced a 1093% increase in ALT and a 348% increase in ALP. In the 3-month study, one of three 300mg/kg/day female dogs experienced markedly elevated ALT and AST values after 6 weeks of therapy but the values returned to normal by week 7 and died at week 9; however no macro or microscopic liver changes were noted on necroscopy. In another 3 month study, one of three 400mg/kg/day males experienced a 2207% increase in ALT and a 152% increase in ALP at day 7 but not at weeks 4, 8, or 13. Necroscopy did not reveal any histopathologic liver changes (Raheja 6/23/06).

In the 13 week desvenlafaxine toxicity study in mice (NDA 21-992), two deaths were noted. At 500mg/kg/day, the male mouse had macroscopic lobular pattern in the liver and microscopic marked acute hepatic necrosis hepatic diffuse hypertrophy at 500/300 mg/kg/day. At final necropsy, the incidence of the incidence of liver hypertrophy was 4%, 7%, 4%, and 13% in males given 0, 50, 150, and 500/300 mg/kg/day, respectively. The investigators noted that the increased incidence of diffuse hypertrophy of the liver may represent an increased incidence due to aging. The microscopic hepatic changes were not seen in rats and dogs. In the 3 month dog study, a moderately increased (27%

compared with controls) adjusted (for final body weight) group mean liver weight was observed in females at 300 mg/kg/day.

Dose-related effects were seen in repeat dose duloxetine animal studies for rats and dogs. “Important toxicologic effects in rats following the dietary administration of duloxetine hydrochloride for 1, 3, or 6 months occurred primarily in the high-dose group of 0.08% or approximately 50 mg/kg. These effects were.... moderate hepatic microsomal enzyme induction with correlated increased liver weights; and minimal-to-moderate midzonal hepatocellular lipid vacuolation primarily in males.” “Hepatic microsomal enzyme induction, increased liver weight, increased liver phospholipid phosphorus, and increased numbers of secondary lysosomes” were seen in the 1, 6, and 12 month dog studies and were limited primarily to the 30-mg/kg group (Pohland 10/01). The effect on hepatic microsomal induction is noteworthy when considering the potential for drug-drug interactions that may result in liver injury.

1.5 SNRI CLINICAL TRIALS

Hepatic effects were also seen in the human clinical trials for venlafaxine, desvenlafaxine, and duloxetine.

Venlafaxine

In the Phase II and III venlafaxine clinical trials, one subject experienced elevated liver enzymes and jaundice (Victoria, 11/22/93, Table 19). Serum ALT values were not included in the routine tests and were only performed at the discretion of the investigator. Potential clinical significance was defined as ALT, AST and ALP ≥ 3 times the upper limit of normal (ULN) and bilirubin ≥ 1.5 times ULN. Clinical significance was based on the medical judgment of the medical monitor (Sasson 07/29/92, p51-3, 143-4).

None of the patients in the placebo group were considered to have clinically significant hepatic laboratory results. Four of the venlafaxine subjects experienced clinically significant elevations in hepatic laboratory results, including one subject with jaundice; with two of the four prematurely terminating study participation due to the elevations (Victoria, 11/22/93, Table 19 and Table 69). Mean increases of clinical relevance were reported for AST and ALP. Significantly different increases from baseline peaked at 3.06% (n=107) with between 421 to 510 days of venlafaxine therapy. The mean ALP was significantly increased from baseline – 7.49% -with the same duration of therapy and increased to a peak increase of 17.75% (n=44) with >780 days of therapy (Victoria, 11/22/93, Summary Table 1).

Desvenlafaxine

In the desvenlafaxine clinical trials for MDD (NDA 21-992) a higher proportion of subjects developed significant⁸ ALT elevations compared to the placebo and venlafaxine groups. For liver enzymes (ALT, AST, and alkaline phosphatase), three (3) times the upper limit of normal was considered potentially clinically significant. For bilirubin, 1.5

⁸ ALT, AST and alkaline phosphatase 3X upper limit of normal (ULN) and bilirubin 1.5 X ULN

times the upper limit of normal was considered potentially clinically significant. “Significant” serum ALT elevations were reported for 0.6% for desvenlafaxine, 0.1% for placebo, and 0 in the venlafaxine group. Statistically significant dose-related changes in the mean were noted for serum AST - increased by 7.6%, ALT - increased by 9.4%, ALP – increased by 10.1%, GGT – increased by 26.8% - and bilirubin - decreased by 17.4% (Levin 10/14/06).

An increase in discontinuation related to elevated liver enzymes was seen in 13 of 1211 desvenlafaxine patients (1.07%), 7 of 803 placebo patients (0.87%), and 1 of 244 venlafaxine patients (0.41%). In the open-label long-term trials, approximately 1% of patients discontinued desvenlafaxine due to elevated liver enzymes. Two of the 13 cases of elevated liver enzymes were considered associated with desvenlafaxine by the investigators. The enzymatic abnormalities resolved with discontinuation and the patients’ bilirubin levels remained within normal limits. The clinical trials did not include any cases that met Hy’s law criteria (Levin 10/24/06).

In the desvenlafaxine clinical trials for menopausal vasomotor symptoms (NDA 21-966), one subject (0.24%) in the placebo group, and nine subjects in all desvenlafaxine groups (0.93%) had increased liver tests greater than 3 times the upper limit of normal. The levels in the placebo patient normalized. One subject in the placebo group⁹ and three in the desvenlafaxine groups had increased liver tests greater than 5 times the upper limit of normal. Viral tests were negative in one venlafaxine subject and data was insufficient to rule out viral causes in the remaining two venlafaxine subjects. One of the desvenlafaxine subjects had severe acute hepatitis with AST and ALT > 25 x ULN and bilirubin > 12 x ULN after approximately six months of therapy. (See below for further information regarding this case.) Four of the subjects prematurely discontinued study participation due to elevated liver tests >3 x ULN. The patient was considered for a liver transplant; however, she improved and her lab values were normal after seven months (Furlong 04/10/07).

OSE reviewed the cases of elevated liver enzymes in NDA 21-966. OSE identified one case of jaundice, which met Hy’s Law criteria (FDA 10/07). An excerpt of the analysis is included below (Senior 3/28/07).

“The course of this woman’s liver test abnormalities suggests acute hepatocellular injury, with an onset about 4 months after initial exposure to the drug, with jaundice following discontinuation of desvenlafaxine fulfilling criteria for a “Hy’s Law” case, or one that is potentially serious and may indicate that other patients may have worse outcomes if exposed to the drug. This case may be an important indicator of possible serious hepatotoxicity risk from this drug, rare but potentially severe, and more likely to occur after prolonged administration of the drug, rather than in the first few weeks” (Senior 03/28/07).

⁹ Isolated elevation of AST>5XULN that normalized rapidly

OSE requested additional information including the complete work-up and all of the test results after the subject was removed from the study until seven months later when her laboratory values normalized. See Appendix 8.8 for additional information from the OSE review.

DPP concluded, “Studies identified possible long-term serious effects of DVS. Of most concern were those effects that cannot be self-diagnosed and may be permanently disabling or lethal, including • Cardiac ischemia • Acute liver toxicity. It is difficult to balance the benefits of treating a common, non-life-threatening symptom with the risks of serious adverse events. DVS does not have to be risk-free. Effective drugs generally are not. However, the benefits of a drug should outweigh its risks. The applicant proposes to use DVS for a non-life-threatening indication for which other therapies, and likely more effective therapies, exist. In this setting, DVS should have a reasonably benign safety profile (Furlong 04/10/07, executive summary).”

Duloxetine

During the clinical trials for duloxetine (NDA 21-427), thirty-one patients discontinued study participation due to elevated transaminases, 0.4%. Elevated ALTs >3 X ULN were seen in 1% of duloxetine treated patients compared to 0.2% of placebo treated patients (Stone 08/02/05). Four subjects had laboratory value abnormalities meeting a modified Hy’s law criteria¹⁰ (Johnson 01/27/05).

1.6 OSE POSTMARKETING REVIEW

In February of 1999, OSE reviewed antidepressants, including venlafaxine, and hepatic failure. The venlafaxine reporting rate for liver failure was 1.8 per 1,000,000 person years (Bennett, 1999).

1.7 SNRI PRODUCT LABELING

Current Venlafaxine Labeling (Effexor 02/08)

The current venlafaxine label (Effexor Rev 02/08) lists hepatotoxic events in the pre and postmarketing adverse event sections of the label. The label recommends a 50% dose reduction in patients with mild to moderate pre-existing hepatic disease. In February 2005, liver necrosis was added to the Overdosage/Human Experience section following the publication of a fatal venlafaxine overdose with toxicology reports revealing only an elevated serum level of venlafaxine (Katz 2005). Venlafaxine does not have hepatotoxicity labeling in the Warnings and Precautions section and does not contraindicate the use of alcohol as does duloxetine. (See below.)

Clinical Pharmacology Pharmacodynamics

Preclinical studies have shown that venlafaxine and its active metabolite O-desmethylvenlafaxine (ODV), are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake.

¹⁰ ALT >3X ULN and total bilirubin >1.5X ULN

Venlafaxine Drugs that Inhibit Cytochrome P450 Isoenzymes - CYP2D6 Inhibitors

In vitro and in vivo studies indicate that venlafaxine is metabolized to its active metabolite, ODV, by CYP2D6, the isoenzyme that is responsible for the genetic polymorphism seen in the metabolism of many antidepressants.

Venlafaxine Clinical Pharmacology - Liver Disease

In 9 subjects with hepatic cirrhosis, the pharmacokinetic disposition of both venlafaxine and ODV was significantly altered after oral administration of venlafaxine. Venlafaxine elimination half-life was prolonged by about 30%, and clearance decreased by about 50% in cirrhotic subjects compared to normal subjects. ODV elimination half-life was prolonged by about 60% and clearance decreased by about 30% in cirrhotic subjects compared to normal subjects. A large degree of intersubject variability was noted. Three patients with more severe cirrhosis had a more substantial decrease in venlafaxine clearance (about 90%) compared to normal subjects. In a second study, venlafaxine was administered orally and intravenously in normal (n = 21) subjects, and in Child-Pugh A (n = 8) and Child-Pugh B (n = 11) subjects (mildly and moderately impaired, respectively). Venlafaxine oral bioavailability was increased 2-3 fold, oral elimination half-life was approximately twice as long and oral clearance was reduced by more than half, compared to normal subjects. In hepatically impaired subjects, ODV oral elimination half-life was prolonged by about 40%, while oral clearance for ODV was similar to that for normal subjects. A large degree of intersubject variability was noted. Dosage adjustment is necessary in these hepatically impaired patients

Venlafaxine Special Populations - Dosage for Patients with Hepatic Impairment

Given the decrease in clearance and increase in elimination half-life for both venlafaxine and ODV that is observed in patients with hepatic cirrhosis and mild and moderate hepatic impairment compared to normal subjects, it is recommended that the total daily dose be reduced by 50% in patients with mild to moderate hepatic impairment. Since there was much individual variability in clearance between subjects with cirrhosis, it may be necessary to reduce the dose even more than 50%, and individualization of dosing may be desirable in some patients.

Venlafaxine Other Adverse Events Observed During the Premarketing Evaluation of Effexor and

Digestive system: Rare: hepatitis, jaundice Metabolic and nutritional: Infrequent: alkaline phosphatase increased, SGOT (AST) increased, SGPT (ALT) increased, Rare: bilirubinemia,

Venlafaxine Postmarketing Reports

hepatic events (including GGT elevation; abnormalities of unspecified liver function tests; liver damage, necrosis, or failure; and fatty liver)

Venlafaxine Overdosage - Human Experience

In postmarketing experience, overdose with venlafaxine has occurred predominantly in combination with alcohol and/or other drugs. The most commonly reported events in overdose include liver necrosis, and ...death have been reported.... Published retrospective studies report that venlafaxine overdose may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants.

Current Desvenlafaxine Labeling (Pristiq 02/29/08)

Desvenlafaxine does not recommend any dose reduction for patients with hepatic insufficiency. Liver necrosis is listed under postmarketing overdose. The labeling does not include any hepatic warning or precautions and does not contraindicate alcohol as does duloxetine.

Desvenlafaxine Metabolism and Elimination

Desvenlafaxine is primarily metabolized by conjugation (mediated by UGT isoforms) and, to a minor extent, through oxidative metabolism. CYP3A4 is the cytochrome P450 isozyme mediating the oxidative metabolism (N-demethylation) of desvenlafaxine. The CYP2D6 metabolic pathway is not involved, and after administration of 100 mg, the pharmacokinetics of desvenlafaxine was similar in subjects with CYP2D6 poor and extensive metabolizer phenotype.

Desvenlafaxine Dosage and Administration

Recommended dose: 50 mg once daily with or without food. There was no evidence that doses greater than 50 mg/day confer any additional benefit.

Hepatic Impairment: dose escalation above 100 mg/day is not recommended (2.2)

Desvenlafaxine Use in Specific Populations Hepatic Impairment

The mean t_{1/2} changed from approximately 10 hours in healthy subjects and subjects with mild hepatic impairment to 13 and 14 hours in moderate and severe hepatic impairment, respectively. No adjustment in starting dosage is necessary for patients with hepatic impairment.

Special Populations Hepatic insufficiency

The disposition of desvenlafaxine succinate after administration of 100 mg was studied in subjects with mild (Child-Pugh A, n = 8), moderate (Child-Pugh B, n = 8), and severe (Child-Pugh C, n = 8) hepatic impairment and to healthy subjects (n = 12).

Average AUC was increased by approximately 31% and 35% in patients with moderate and severe hepatic impairment, respectively, as compared to healthy subjects. Average AUC values were similar in subjects with mild hepatic impairment and healthy subjects (< 5% difference).

Systemic clearance (CL/F) was decreased by approximately 20% and 36% in patients with moderate and severe hepatic impairment, respectively, as compared to healthy subjects. CL/F values were comparable in mild hepatic impairment and healthy subjects (< 5% difference).

The mean t_{1/2} changed from approximately 10 hours in healthy subjects and subjects with mild hepatic impairment to 13 and 14 hours in moderate and severe hepatic impairment, respectively. No adjustment in starting dosage is necessary for patients with hepatic impairment.

Desvenlafaxine Clinical Studies Experience

Other infrequent adverse reactions, not described elsewhere, occurring at an incidence of <2% in MDD patients treated with Pristiq were: **Investigations** – Liver function test abnormal,

Desvenlafaxine Human Experience with Overdosage

There is limited clinical experience with desvenlafaxine succinate overdosage in humans. In pre-marketing clinical studies, no cases of fatal acute overdose of desvenlafaxine were reported.

Current Duloxetine Labeling (Cymbalta 11/28/07)

Duloxetine is extensively labeled for hepatotoxicity in Warnings and Precautions, Special Populations and the Drug Interactions. (See below) Duloxetine is also labeled for a drug interaction with alcohol.

Duloxetine Pharmacokinetics - Metabolism and Elimination

The major biotransformation pathways for duloxetine involve oxidation of the naphthyl ring followed by conjugation and further oxidation. Both CYP1A2 and CYP2D6 catalyze the oxidation of the naphthyl ring *in vitro*.

Duloxetine Warnings and Precautions - Hepatotoxicity

Elevated transaminases, bilirubin and alkaline phosphatase, some severe, have occurred. Cymbalta should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

Hepatotoxicity

Cymbalta increases the risk of elevation of serum transaminase levels. Liver transaminase elevations resulted in the discontinuation of 0.3% (73/23,983) of Cymbalta-treated patients. In these patients, the median time to detection of the transaminase elevation was about two months. In placebo-controlled

trials in any indication, elevation of ALT >3 times the upper limit of normal occurred in 1.1% (75/6871) of Cymbalta-treated patients compared to 0.3% (13/5036) of placebo-treated patients. In placebo-controlled studies using a fixed-dose design, there was evidence of a dose-response relationship for ALT and AST elevation of >3 times the upper limit of normal and >5 times the upper limit of normal, respectively. Postmarketing reports have described cases of hepatitis with abdominal pain, hepatomegaly and elevation of transaminase levels to more than twenty times the upper limit of normal with or without jaundice, reflecting a mixed or hepatocellular pattern of liver injury. Cases of cholestatic jaundice with minimal elevation of transaminase levels have also been reported. The combination of transaminase elevations and elevated bilirubin, without evidence of obstruction, is generally recognized as an important predictor of severe liver injury. In clinical trials, three Cymbalta patients had elevations of transaminases and bilirubin, but also had elevation of alkaline phosphatase, suggesting an obstructive process; in these patients, there was evidence of heavy alcohol use and this may have contributed to the abnormalities seen. Two placebo-treated patients also had transaminase elevations with elevated bilirubin. Postmarketing reports indicate that elevated transaminases, bilirubin and alkaline phosphatase have occurred in patients with chronic liver disease or cirrhosis. Because it is possible that duloxetine and alcohol may interact to cause liver injury or that duloxetine may aggravate pre-existing liver disease, Cymbalta should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

Clinically Important Drug Interactions - Other Clinically Important Drug Interactions

Alcohol—Use of Cymbalta concomitantly with heavy alcohol intake may be associated with severe liver injury. For this reason, Cymbalta should ordinarily not be prescribed for patients with substantial alcohol use.

Duloxetine Dosing in Special Populations - Hepatic Insufficiency

It is recommended that Cymbalta should ordinarily not be administered to patients with any hepatic insufficiency

Use in Specific Populations - Hepatic Insufficiency

Patients with clinically evident hepatic insufficiency have decreased duloxetine metabolism and elimination. After a single 20-mg dose of Cymbalta, 6 cirrhotic patients with moderate liver impairment (Child-Pugh Class B) had a mean plasma duloxetine clearance about 15% that of age- and gender-matched healthy subjects, with a 5-fold increase in mean exposure (AUC). Although C_{max} was similar to normals in the cirrhotic patients, the half-life was about 3 times longer

Use in Patients with Concomitant Illness - Hepatic Insufficiency

Cymbalta should ordinarily not be used in patients with hepatic insufficiency

Duloxetine Drug Interactions - Alcohol

When Cymbalta and ethanol were administered several hours apart so that peak concentrations of each would coincide, Cymbalta did not increase the impairment of mental and motor skills caused by alcohol. In the Cymbalta clinical trials database, three Cymbalta-treated patients had liver injury as manifested by ALT and total bilirubin elevations, with evidence of obstruction. Substantial intercurrent

Duloxetine Overdosage - Signs and Symptoms

In postmarketing experience, fatal outcomes have been reported for acute overdoses, primarily with mixed overdoses, but also with duloxetine only, at doses as low as 1000 mg. Signs and symptoms of overdose (duloxetine alone or with mixed drugs) included somnolence, coma, serotonin syndrome, seizures, syncope, tachycardia, hypotension, hypertension and vomiting.

2 METHODS AND MATERIALS

This section will describe the search criteria used to identify a potential data mining signal, to identify safety reports in the Adverse Event Reporting System (AERS) database, and to identify case reports in the published medical literature. The methods for drug use sourcing and obtaining reporting rates are also described.

2.1 AERS SELECTION OF CASES

OSE has developed a consistent search strategy to identify “liver failure” cases. (See Appendix 8.3) The standardized OSE search strategy below was used to query the AERS database. Cases were obtained from an AERS search of reports from the time of approval through 10/03/2007. Search criteria were as follows:

Table 2: AERS Search Strategy

Drug name search terms:	venlafaxine active ingredient and related verbatim terms Effexor™ trade name
OSE liver failure search strategy (liver failure/cirrhosis): (Wyeth 2007)	HLT – hepatic disorder and associated disorders HLT – hepatic fibrosis and cirrhosis PT – hepatic necrosis PT – hepatitis fulminant PT – liver transplant
Combination products	Included

Case Definition: duplicates, cases reporting intentional overdose, onset of symptoms preceded venlafaxine therapy and rhabdomyolysis or neuroleptic malignant syndrome will be excluded. The remaining cases will be included in the case series.

See Appendix 8.2 for additional AERS data base information.

See Appendix 8.3 for additional OSE Liver Failure Case Definition information.

2.2 DRUG UTILIZATION DATABASES

IMS Health, IMS National Sales Perspectives™ data were used to determine the primary setting in which venlafaxine is sold. Cumulative sales of this product by extended units (tablets) sold from the manufacturer into the various retail and non-retail channels of distribution were analyzed for the years 2002 through 2007. A complete description of this IMS Health database is provided in Appendix 8.4.

Using the wholesale distribution data (IMS Health 02/08), we determined that, on average, sales to retail pharmacies accounted for roughly 73%, non-retail pharmacies (non-federal hospitals, federal facilities, clinics, long term care, HMOs, home health care, and others miscellaneous channels) accounted for approximately 11% and mail order pharmacies roughly 16% of the total number of extended units of venlafaxine sold during the five years examined.

Because most of the product sold during this time period went to retail pharmacies, we examined utilization patterns focusing on the outpatient setting. Sales data indicate that the Verispan retail pharmacy prescription databases are the most appropriate data sources to measure the use of these products among the databases licensed by FDA.

Outpatient use and patient demographics were measured with two data sources from Verispan, LLC: Vector One®: National (VONA), and Total Patient Tracker (TPT). From these sources, nationally projected estimates of the number of prescriptions dispensed by retail pharmacies and the number of patients who received a prescription dispensed by

retail pharmacies for venlafaxine were obtained. Outpatient drug utilization patterns were examined for the fourteen calendar years from 1994 through 2007.

See Appendix 8.4 for additional drug use data base information.

2.3 LITERATURE SEARCH

The literature search was executed to find case reports, case histories, letters, or other documents that described hepatotoxic events that might be associated with venlafaxine use. Dr. Dubitsky had performed a prior review in 2006 (Dubitsky 07/06), so this search focused on articles published since that time. The search terms were:

venlafaxine or Effexor	venlafaxine and liver
venlafaxine and hepat*	venlafaxine and hepatitis

2.4 REPORTING RATES

To calculate reporting rates, the projected total numbers of prescriptions and users overall and by age and gender were obtained from Verispan database (Appendix 8.4). The number of reports was obtained from the AERS database.

Cases were classified as ‘probable’ in causal association, if there was no viable alternate explanation and venlafaxine appeared to be the most likely etiology of hepatotoxic effects. ‘Possible’ cases were defined as those with a viable alternative explanation, but venlafaxine could not be ruled out and may have played a role in the outcome. ‘Unlikely’ cases have a viable alternative explanation that appears to be the more likely explanation for the hepatotoxic effects with venlafaxine having an unlikely role. Duplicate cases and cases that could not be assessed, due to a lack of information, were excluded.

See Appendix 8.5 for additional drug use data.

See Appendix 8.6 for additional information regarding causal association terms.

3 RESULTS

3.1 ADVERSE EVENTS

AERS Cases

The AERS query identified 82 cases, of which 25 were duplicates. One case reported a reaction that occurred prior to venlafaxine therapy, two cases reported neuroleptic malignant syndrome, one case rhabdomyolysis and nine cases reported an intentional overdose. The 13 cases and the 25 duplicates were excluded for a total of 38 exclusions.

The 44 remaining cases are characterized in the table below.

Table 3. Characteristics of Unique AERS Cases of Serious Liver Injury with Venlafaxine from Marketing to 10/03/2007 (n=44)

Location	US (15), Foreign (29)
Report	Expedited (40), Direct (2), Periodic (2)
Primary Outcome ¹¹	Death (21), Hospitalization (23)
Gender	Female (30), Male (11), Not reported (3)
Age	Range (16-86 years old), Median (55 years old), (n=36)
Peak Daily Dose	Range (37.5-300 mg), Median (150 mg), (n=31)

Seven cases contained insufficient information to assess the strength of the relationship between serious liver injury and venlafaxine therapy. In sixteen of the cases, the adverse reaction appears more closely related to a concomitant medication or a comorbid medical condition rather than the venlafaxine therapy; however, a role for venlafaxine cannot be ruled out. The potential concurrent risk factors for the sixteen cases are listed below.

Comorbid conditions which may have contributed to the liver failure

1. Acute cholecystitis (1)
2. Severe cholestasis and bile duct injury (1)
3. Alcohol (4)
4. Cirrhosis/fibrosis (2)
5. Chronic hepatitis C (1)
6. Fatty liver (1)
7. Likely hepatic neoplasm (1)
8. Autoimmune hepatitis (2)
9. Portal vein thrombosis (1)
10. Pregnancy/pre-eclampsia, resolved after delivery (1)
11. Status/post surgical procedure (2)

Concomitant medications that may have contributed to the liver failure

1. Temporal with: dose increase of acetaminophen (1), alverine (1), atomoxetine (1), clarithromycin (1), diclofenac (1), piroxicam/bromazepam (1), telithromycin (1), valproate (1)
2. Positive dechallenge with mirtazapine (1)
3. Positive rechallenge with methotrexate/leflunomide/celecoxib (1), risperidone (1)
4. Idiosyncratic reaction to Darvon (1)

The case series includes 21 cases where the serious liver injury appears more closely related to venlafaxine than a comorbid medical condition or a concomitant medication. The year of receipt and the clinical characteristics of the case series are summarized in Tables 4 and 5. The Guidance for Industry Drug-Induced Liver injury

¹¹ Priority – Death, hospitalization, life threatening, required intervention, disability, congenital anomaly

Table 4. Year Received by the FDA for Unique AERS Cases of Serious Liver Injury with Venlafaxine from Marketing to 10/03/2007 (n=21)

Year Received by the FDA	# of cases
1995	1
1996	1
1998	2
2000	1
2001	2
2002	3
2003	1
2004	4
2005	1
2006	1
2007	4
*Total	21

Table 5. Clinical Characteristics of Unique Cases of Serious Liver Injury with Venlafaxine Therapy

Peak Daily Dose	Range (75-300mg), Median (150mg), (n=17)
Unchanged Dose – Time to Onset	Range (4-1994 days) Median (25 days) (n=12), also “over a month”
Dose Increase – Time from peak dose to Onset	15 days, 33 days, approx 4-5 weeks, approx 2-3 months (n=4)
Reported Diagnosis	acute hepatic failure (1), acute hepatitis (1), acute liver failure (1), acute hepatic necrosis (1), cytolytic hepatitis (1), drug-induced hepatitis (1), fulminant hepatic failure (5), fulminant hepatitis (3), hepatic encephalopathy (1), hepatic failure (3), hepatorenal syndrome (1), jaundice & hepatic necrosis (1), liver failure (1),
Type of Liver Injury* (Lee 2005)	Hepatocellular (7), Mixed (1), Cholestatic (1), Not Reported (12)
Serum ALT between >3xULN & <5xULN** & Bili>2xULN	(n=2)
Serum ALT between >5xULN & <10xULN & Bili>2xULN	(n=0)
Serum ALT between >10xULN & <20xULN & Bili>2xULN	(n=2)
Serum ALT>20xULN & Bili>2xULN	(n=9)
Serum ALT>3xULN, Bili>2xULN & ALP<2xULN	(n=5)

*if normal range not reported, 100 U/L used for ALP ULN, * if normal range not reported, 40 U/L used for ALT

The most compelling case (summarized below) describes a case of hepatotoxicity in a patient without concomitant medications or comorbid medical conditions that may have contributed to the liver injury.

ISR # 4536028, FDA Received Date 12/16/2004, Onset of Event (b) (6)

A nurse practitioner reported the case of a 35 year old female who started Effexor XR 150mg daily to treat anxiety and depression. The patient was not taking any concomitant medications. On (b) (6) the patient was evaluated for complaints of fatigue, nausea, and vomiting, and diagnosed with fulminant hepatic failure. The patient was transferred from the ER to another hospital where she was admitted to the ICU for mild encephalopathy, elevated transaminases that peaked in the 8,000s, and an elevated bilirubin that peaked in the 4s. A transjugular liver biopsy was performed and revealed moderate to severe inflammation with a mixture of lymphocytes, neutrophils, and eosinophils. No significant plasma cell population was identified. Severe piecemeal necrosis with periportal hepatocyte dropout was seen with the remaining hepatocytes showing moderate to severe steatosis. A trichrome stain highlighted the areas of hepatocyte drop out; however, there was no increase in collagen fibrosis. An iron stain showed a mild increase in iron stores and PAS and PAS/D were unremarkable. The copper stain was non-contributory. Viral serology was negative, as well as the ANA and anti-smooth muscle antibody. During the course of her admission, the encephalopathy resolved, the transaminases declined with the AST in the 100s and the ALT around 1500 on discharge. The bilirubin and international normalized ration (INR) were trending toward normal at discharge. On (b) (6), the patient was discharged with directions to follow-up with a gastroenterologist. The patient was not prescribed any medication. Per verbal follow-up with the gastroenterologist's nurse, on (b) (6), the patient's total bilirubin was 0.7, ALT 16, AST 21, and ALP 68. The patient had no history of hepatic risk factors such as alcohol abuse or exposure to mushrooms. A potential alternate etiology for the serious liver injury was not identified.

Twenty of the twenty-one AERS cases in the case series report comorbid medical conditions or concomitant medications, which may have contributed to the liver failure; however, a role for venlafaxine cannot be ruled out. (See Appendix 8.9) One of the twenty-one was diagnosed with a cytochrome P450 problem, which was not defined, but was reportedly the cause of the increased serum level of venlafaxine and the liver failure. Five patients in the case series described a history of alcohol abuse.

Twelve of twenty-one cases resulted in death. One death occurred after a failed liver transplant. A hepatic related cause of death was reported in six additional cases: fulminant hepatitis (2), liver failure associated with mirtazapine and venlafaxine (1), hepatorenal syndrome/myocardial ischemia (1), hepatic failure (1), and acute liver necrosis and coronary artery disease (1). Four of the twenty-one cases indicated that the venlafaxine dose had been increased, prior to the onset of the liver failure. A representative case is summarized below.

ISR # 3160091, FDA Received Date 11/20/1998, Date of Event (b) (6)

Information was obtained from the Swedish MPA and the physician. A 45 year old female was prescribed venlafaxine 37.5mg BID to treat anxiety and severe social phobia. Over a period of 10 months, the dose was gradually increased to 300mg daily. On Day 26, after the last dose increase, the patient experienced severe nausea for one week and on Day 33 was instructed to decrease the venlafaxine to 75mg daily. The patient was hospitalized on (b) (6) with a history of increasing icterus and dark urine for 3 days and abdominal pain, fatigue, nausea and headache for 1-2 weeks. On admission, her laboratory values were as follows: ALT 67.6x ULN, AST 47.3x ULN, ALP 1.62x ULN and total bilirubin 7.6x ULN. The patient's liver tests had been normal. The patient developed fulminant hepatic failure, and subsequently died after an unsuccessful liver transplant. Concomitant medications, orphenaderin, propiomazine, alprazolam, naproxen, and buspirone, had been taken for more than a year. Flupenthixol had been taken for 9 months prior to the onset of liver failure and was gradually decreased from 2mg to 1mg after venlafaxine was prescribed. As the patient had not reported paracetamol use on admission, no levels were drawn. Subsequently, she reported 1500-2000mg of paracetamol but repeatedly denied using more than 2000mg.

See Appendix 8.9 for additional case information.

Medical Literature Cases

Dr. Dubitsky's search of the medical literature identified five cases of 'probable' venlafaxine hepatotoxicity (Dubitsky 07/12/06). These five cases are not included in the twenty-one venlafaxine cases from AERS. The ages ranged from 30-78 years with a median of 44 years. Of note is a positive dechallenge case that occurred with low dose venlafaxine therapy. Dr. Dubitsky's summary of the case is included below. Four of the five articles recommend monitoring of liver functions. The fifth article, Phillips et al., recommends early consideration of venlafaxine-induced hepatitis in symptomatic patients, regardless of the dose.

See Appendix 8.7 for the summary of the remaining four cases.

"Phillips (Phillips et al 2006) and coworkers published a report of a 60 year old woman who was treated with venlafaxine 75 mg/day for one month for postmenopausal vasomotor symptoms. At that time, she presented with nonspecific complaints, including right upper quadrant abdominal pain. Workup revealed an enlarged liver on ultrasound and markedly elevated liver functions tests: ALT 372 U/L (normal 0-20), AST 99 U/L (normal 0-31), and alkaline phosphatase 483 U/L (normal 35-104); GGT two days later was also substantially increased (962 U/L, normal 5-36). Laboratory tests, including hepatitis serologies, were negative. Alcohol use was reported as one glass of beer or wine, three or four times per week prior to symptom onset. Concomitant medications included acetaminophen 1,000mg tid. Venlafaxine and other medication possibly related to hepatotoxicity were stopped and, within one week, liver function tests and clinical symptoms were significantly improved. Four weeks after discontinuing venlafaxine, it was restarted at a dose of 37.5 mg/day. Five days after resuming venlafaxine therapy, her transaminase levels were again elevated (ALT 269, AST 49, GGT 256, and alkaline

phosphatase 263 U/L). Alcohol consumption and acetaminophen use were not resumed during this rechallenge with venlafaxine. Liver function abnormalities returned to near baseline levels two weeks after discontinuing venlafaxine. This case is remarkable given the association of hepatitis with low dose venlafaxine and the positive rechallenge.” (Dubitsky 07/12/06)

3.2 **DRUG UTILIZATION DATA**

3.2.1 **Retail Prescriptions**

The projected number of venlafaxine prescriptions dispensed in the U.S. by retail pharmacies was obtained using Verispan’s Vector One: National (Appendix 8.5, Table 1). The number of prescriptions dispensed rose from approximately 1.2 million during year 1994 to about 18.7 million dispensed during year 2007. Prescriptions for venlafaxine have steadily increased since marketing. The only decline in dispensed prescriptions was between years 2005 and 2006.

3.2.2 **Retail Patient Counts**

The projected number of patients receiving a venlafaxine prescription dispensed through a U.S. retail pharmacy was obtained using Verispan’s Total Patient Tracker (Appendix 8.5, Table 2). The total patient count data was available from years 2002 to 2007. The projected number of patients who received a prescription has been relatively declining since year 2003. By year 2007, approximately 3.3 million patients have received a prescription for venlafaxine in U.S. retail pharmacies.

See Appendix 8.5 for additional drug use data.

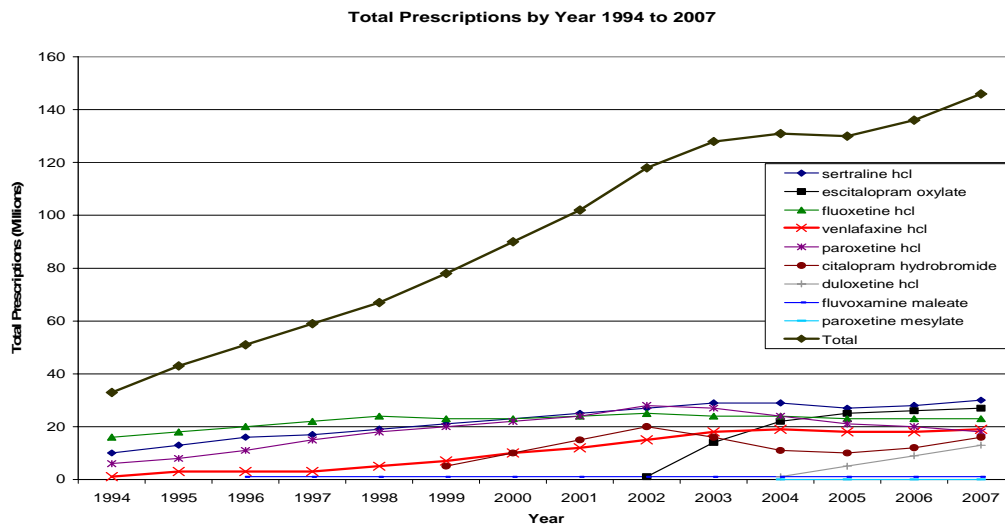
3.3 **LITERATURE SEARCH RESULTS**

The literature searches did not unearth any new case reports in addition to those reviewed previously by Dr. Dubitsky. A 2003 WHO data mining investigation found that hepatic events associated with venlafaxine were not reported more often than expected when compared to selective serotonin reuptake inhibitors, but concluded that the findings were preliminary due to the investigative nature of data mining (Spigset, Hägg, & Bate, 2003).

3.4 **REPORTING RATES**

Figure 2 shows the yearly projected prescribing levels for venlafaxine as compared to other selective serotonin reuptake inhibitors (SSRI) and SNRIs. The number of prescriptions for venlafaxine has remained steady, between 15 and 19 million per year, since 2002. When compared to other SSRI and SNRI products, venlafaxine is one of the more commonly used drugs. Since 2002, approximately 3.2 to 3.8 million projected unique individuals have been prescribed venlafaxine every year (Verispan 2002-07). See Appendix 8.5, Table 2)

Figure 2. Yearly Projected Prescribing Levels (Verispan 1994-2007)



Drug Utilization Data Tables

Table 1. Projected Number of Venlafaxine Prescriptions Dispensed by U.S. Retail Pharmacies, 1994-2007

	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
	Retail TRxs	Retail TRxs	Retail TRxs	Retail TRxs	Retail TRxs	Retail TRxs	Retail TRxs	Retail TRxs	Retail TRxs	Retail TRxs	Retail TRxs	Retail TRxs	Retail TRxs	Retail TRxs
TOTAL MARKET	1,220,539	2,561,115	3,182,335	3,459,793	4,874,894	7,394,096	10,043,365	12,277,510	15,330,235	17,984,351	19,197,456	18,348,934	18,288,679	18,692,277

Source: Verispan Vector One: National, Data Extracted 2-08, File VONA venlafaxine TRx 94 to 07.xls

Table 2. Projected Number of Patients Receiving Venlafaxine through U.S. Retail Pharmacies for the Years 2002-2007

	2002		2003		2004		2005		2006		2007	
	Patient Count	%	Patient Count	%	Patient Count	%	Patient Count	%	Patient Count	%	Patient Count	%
Total	3,208,229	100.00%	3,861,372	100.00%	3,682,968	100.00%	3,391,091	100.00%	3,352,765	100.00%	3,347,807	100.00%
Effexor	474,812	14.80%	472,624	12.24%	392,035	10.64%	349,458	10.31%	281,611	8.40%	42,226	1.26%
Effexor XR	2,916,013	90.89%	3,564,758	92.32%	3,436,847	93.32%	3,170,446	93.49%	3,123,663	93.17%	3,064,135	91.53%
venlafaxine									156,696	4.67%	405,976	12.13%

Source: Verispan Vector One: Total Patient Tracker, Data Extracted 2-08, File TPT venlafaxine patient count 02 to 07.xls

The average days of therapy for a prescription was approximately 25 in 1994, the first year of marketing, but increased to 30 by 2001, and has remained at that level until 2007. There were six domestic AERS cases between 1995 and 2007 in which a role for venlafaxine could not be ruled out, one with a ‘probable’ causal association and five with a ‘possible’ causal association with venlafaxine.

Domestic adverse event reporting rates were calculated from 2002 through 2007. This time period was chosen because data on the projected unique number of patients was available starting in 2002. For the entire period that venlafaxine has been marketed in the US, there were never more than two reports of liver failure in a single year.

Rates were calculated by obtaining the total projected number of prescriptions and projected average days of therapy from Verispan’s VONA database. Verispan data are described in detail in Appendix 8.4. Person-years of exposure were calculated using the following formula: (total number of dispensed prescriptions X average days of therapy) ÷

365. Reporting rates per 100,000 person-years were calculated using the following formula: (reports of adverse events during the specified time ÷ estimated person-years of exposure) X 100,000.

Table 6 shows the reporting rate for all events that were classified as ‘probable’ or ‘possible.’ Because of the low numbers of events, further stratification by age or gender was not done.

Table 6. Overall Domestic Reporting Rates for ‘Probable’ and ‘Possible’ Venlafaxine Causally Associated Reports of Serious Liver Injury, 2002 – 2007.

	2002	2003	2004	2005	2006	2007
Projected Total Rx’s*	15,330,235	17,984,350	19,197,454	18,348,936	18,288,675	18,692,277
Projected Days of Therapy*	30	30	30	30	31	31
Person-Years of Exposure	1,260,019	1,488,020	1,593,652	1,611,528	1,528,232	1,572,200
Reported Adverse Events	0	1	1	1	0	0
Reporting Rate/100,000 Person-Years	0.00	0.07	0.06	0.06	0.00	0.00

*Source: Verispan, LLC, Vector One: National Years 2002 – 2007, extracted Feb 08. File: venlafaxine DOT 94 to 2K7.xls

The reporting rates for liver failure events have remained constant throughout the past few years. No trend was seen towards either higher or lower levels of events. There have never been more than two events reported in a single year since venlafaxine was first marketed.

4 DISCUSSION

The purposes of this consult were to conduct a literature search specifically for finding hepatic events that were possibly associated (Uppsala Monitoring Centre) with venlafaxine use, to present reporting rates for liver failure associated with venlafaxine and to provide an analysis of venlafaxine’s hepatotoxicity in AERS postmarketing cases.

Venlafaxine has been on the market now for approximately 15 years. The first indication of venlafaxine’s potential liver effects was seen in the animal studies. Abnormal serum ALT and AST values were seen in dogs and monkeys; as well as increased liver weights in dogs. During the human clinical trials, seven patients discontinued study participation due to abnormal hepatic laboratory values with one subject experiencing jaundice and hepatitis. OSE identified 26 postmarketing cases of serious liver injury potentially associated with venlafaxine therapy, 21 from AERS, and 5 from the medical literature. Venlafaxine’s potential link to a risk for serious liver injury is supported by one case in the medical literature that describes a positive rechallenge at low dose therapy. In addition, six cases with a ‘probable’ causal association were identified, including four cases from the medical literature and two cases from AERS. The case series includes nineteen AERS cases with a ‘possible’ causal association with venlafaxine. (See Appendices 8.6, 8.7 and 8.9)

A PubMed search was performed that focused on case reports, case series, and letters that discussed hepatic events associated with venlafaxine. Of particular interest were any reports published after a 2006 review by Dr. Dubitsky. No additional documents were found beyond the ones described in his report.

Domestic reporting rates were calculated based on AERS reports of hepatic events associated with venlafaxine for the period of 2002 to 2007. Verispan's VONA and TPT data resources were used to provide information on the projected total number of prescriptions, average days of therapy per prescription, and the projected total number of unique patients prescribed this drug. There did not seem to be either a significantly elevated reporting level or trend in reporting towards either higher or lower rates. Due to the low numbers of AERS cases found, it was not possible to further stratify reports by age or gender. Domestic reporting rates calculated for 2002 through 2007 did not show an elevated level of reporting or a trend in reporting rates towards higher or lower values.

Adverse event reporting rates have several limitations. Most importantly, there may be significant underreporting of adverse events. The FDA uses a passive reporting system, which required that the event be detected, be attributed to the drug, and be reported to either the manufacturer or the FDA directly. It is possible that some adverse events occurred that were not attributed to venlafaxine use, or were not reported. In addition, the background hepatic event rate in this group of individuals is not known; therefore, no conclusions should be drawn from these rates. Based on this information, no additional measures can be recommended. If new cases or data become available regarding this association, the situation should be re-evaluated.

The reporting rate was consistent with the expected results. Although venlafaxine has been on the market for approximately 15 years and has been widely prescribed, OSE had not previously identified an increased number of serious liver injury cases. This review was prompted by the sponsor's identification of five published cases of 'probable' venlafaxine-induced liver injury. Although, the number of serious liver injury cases with venlafaxine therapy is not large, and appears to be below the background rate, the serious outcomes, including death, are a cause for concern. Seven cases reported a liver related cause of death, including one death after a failed liver transplant. The "probable" causal association of venlafaxine with serious liver injury prompted four of the five authors of published cases to recommend monitoring of liver functions, particularly for patients with pre-existing liver disease. In addition, two of the articles note that clinicians should be aware of and consider venlafaxine hepatotoxicity in symptomatic patients.

OSE also reviewed the hepatotoxicity of the remaining SNRIs, desvenlafaxine, and duloxetine. Desvenlafaxine is a succinate salt of the primary metabolite of venlafaxine. Desvenlafaxine was compared to a placebo and to venlafaxine in the clinical trials. One subject in the desvenlafaxine vasomotor symptoms clinical trials experienced elevated liver tests including ALT values elevated 25x ULN. Dr. Senior noted that this case fulfilled Hy's Law criteria. Desvenlafaxine was recently approved to treat MDD; however, DPP considered the application for vasomotor symptoms unapprovable and

noted, “It is difficult to balance the benefits of treating a common, non-life-threatening symptom with the risks of serious adverse events” (Furlong 04/10/07 executive summary).

Desvenlafaxine was approved February 28, 2008, which limits the adverse event data available to the FDA. There are currently no postmarketing serious liver injury reports in AERS; therefore, AERS cannot be used to assess desvenlafaxine’s potential for serious liver injury. However, desvenlafaxine is a succinate salt of ODV, the major metabolite of venlafaxine and thus, is similar in chemical structure to venlafaxine. In addition, the liver injury in the desvenlafaxine clinical trials, coupled with the serious liver injury associated with venlafaxine, further supports the concern of a potential increased risk of serious liver injury with desvenlafaxine therapy.

Duloxetine has been on the market for approximately 4 years. The hepatotoxicity associated with duloxetine therapy is recognized and labeled in the Warning and Precautions section; however, an unconfounded case has not been reported to the FDA or described in the medical literature. DPP is in the process of strengthening the hepatotoxicity warning in the label (Stone 02/08).

The Guidance for Industry for labeling indicates that a serious adverse reaction “for which there is reasonable evidence of a causal association between the drug and the adverse reaction” should be included in the Warning and Precautions. Serious is defined as any adverse reaction resulting in death, a life-threatening adverse experience, or inpatient hospitalization (FDA 2006). Duloxetine, venlafaxine, and desvenlafaxine meet these criteria. DPP considered the desvenlafaxine “acute liver toxicity” in the clinical trials for NDA 21-966 to be a “serious safety issue” and indicated that drug treating a non-life-threatening indication for which other therapies, and likely more effective therapies, exist should have a reasonably benign safety profile (Furlong 04/10/07 executive summary).

5 CONCLUSION

Based on a review of the animal studies, the clinical trial data, and adverse events from the medical literature and AERS, the three SNRIs, venlafaxine, desvenlafaxine, and duloxetine, appear to be linked to a risk for clinically serious idiosyncratic hepatotoxicity. Duloxetine is labeled in the Warning and Precautions section for hepatotoxicity; however, venlafaxine and desvenlafaxine are not. Venlafaxine does not have a large number of reports of serious liver injury; however, the positive rechallenge at low dose therapy and six cases with a ‘probable’ causal association support venlafaxine’s hepatotoxicity. The desvenlafaxine clinical trials highlight a potential for serious liver injury.

Venlafaxine has listings of hepatotoxic events in the Other Adverse Events Premarketing section and the Postmarketing Reports section. Desvenlafaxine has a listing of “liver function test abnormal” in the Other Adverse Reactions section. The current labeling for venlafaxine and desvenlafaxine does not appear sufficient to alert health care providers of the potential for serious liver injury. Labeling should be modified for both drugs to

convey the ‘possible’ risk for serious liver injury. In addition, early notification of potential cases of serious injury with SNRI therapy will allow the FDA to efficiently monitor the potential public health risk and respond in a timely manner.

6 RECOMMENDATIONS

Therefore, OSE recommends:

1. Request that the SNRI sponsors to use 15-day reporting of all elevated transaminase levels with elevated bilirubin levels, clinical jaundice or serious liver injury e.g., hepatitis, liver failure, hepatic necrosis
2. Request that the SNRI sponsors to monitor for liver toxicity and actively pursue follow-up for any reports of elevated transaminase levels with elevated bilirubin levels, clinical jaundice or serious liver injury e.g., hepatitis, liver failure, hepatic necrosis
3. Add labeling to the Warning and Precautions section for venlafaxine and desvenlafaxine indicating the ‘possible’ risk of serious liver injury.
4. Add labeling in the Information for Patients section and the Medication Guide to instruct patients to discontinue the SNRI and contact their primary care physician if they experience dark urine or a yellow discoloration of the eyes, inside of the mouth, or skin.

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8 APPENDICES

8.1 WEBVDME DATA MINING TOOL

A data mining search of the AERS database was performed for this analysis using WebVDME 6.0. This method uses the Multi-item Gamma Poisson Shrinker (MGPS)¹²⁻¹³ algorithm which analyzes the records contained in the AERS database. The algorithm then quantifies reported drug-event associations by producing a set of values or scores which indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting rate of an event for a particular drug relative to all other drugs and events in the database. MGPS also calculates lower and upper 90% confidence limits for the EBGM values, denoted as EB05 and EB95 respectively.

8.2 LIMITATIONS OF AERS

The voluntary or spontaneous reporting of adverse events from health care professionals and consumers in the U.S reflects underreporting and also duplicate reporting. For any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s). The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues. Therefore, counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing drug risk between drugs.

8.3 CASE DEFINITION, LIVER ACUTE INJURY

OSE WORKING CASE DEFINITIONS FOR POSTMARKETING ADR REVIEW, Acute Liver Injury

II. ODS Case Definition⁸—The following case definition was adapted from a case definition previously developed within the Office of Drug Safety to categorize the extent of drug-induced liver injury.⁷

⁸ The case definition can be adapted as needed, depending on the requirements of the consult. Examples of adaptations of this definition are presented in Attachments 1 and 2.

Category 1: Very mild or poorly characterized liver injury—Serum ALT or AST elevated but <3 times the upper limit of normal* (ULN); normal TB and prothrombin time (PT).

*ULN varies depending on the laboratory, but the following can be used as a guide for ULN: AST ~42 IU/L, ALT ~30 IU/L, TB ~1 mg/dL

Category 2: Mild-to-moderate liver injury—serum transaminase elevations with no evidence of overall liver function loss. This may also include reports of hepatitis NOS, with no lab data and reports of elevations in transaminases without signs or symptoms of overall loss of liver function. Further sub-categorization can be determined using the following:

Mild: At least 3 x ULN ALT or AST but <10x ULN; normal bilirubin and PT.

Moderate: At least 10 x ULN ALT or AST; normal bilirubin and PT.

Category 3: Moderately severe liver injury—liver injury causing acute impairment of liver function w/inability to make enough PT or clear bilirubin from the blood sufficiently. Impaired liver function without liver failure. Reported clinical signs or symptoms might include jaundice, coagulopathy, and elevated bilirubin. Further sub-categorization can be determined using the following:

A. Possibly threatening: At least 3x ULN ALT or AST and (elevation of bilirubin to <3 x ULN or PT (INR) to < 1.5).

B. Definitely threatening: At least 3x ULN ALT or AST and INR > 1.5 or bleeding events (hematuria, bleeding gums, etc.), or jaundice or elevation of bilirubin to at least 3 x ULN

Category 4: Severe life-threatening injury with liver failure—severe liver injury with secondary impairment of brain or kidney function. Death, liver transplantation, placement on a liver transplant list, or evidence of altered mental status (encephalopathy) in the setting of acute liver injury (elevated transaminases, bilirubin, or jaundice). Reported clinical signs and symptoms may include coagulopathy or renal function impairment. This category will also include reports with a diagnosis of liver failure without supporting clinical or laboratory data. The biggest distinction between 3 and 4 is neurologic and kidney involvement. This will also include reports with a diagnosis of liver failure without supporting clinical or laboratory data.

III. AERS search strategy (MedDRA 4.0)

- ODS Reaction Groups
- For all liver injury—*ODS Liver All*
- *Hepatic and hepatobiliary disorders (HLGT)*
- *Hepatobiliary investigations (HLGT)*
- *Liver transplant (PT)*
- For liver failure cases—*ODS Liver failure/cirrhosis*
- *Hepatic failure and associated disorders (HLT)*
- *Hepatic fibrosis and cirrhosis (HLT)*
- *Hepatic necrosis (PT)*
- *Liver transplant (PT)*
- *Hepatitis fulminant (PT)*

8.4 DRUG UTILIZATION DATABASE DESCRIPTIONS

IMS Health, IMS National Sales PerspectivesTM; Retail and Non-Retail

The IMS Health, IMS National Sales PerspectivesTM measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

Verispan, LLC: Vector One[®]; National (VONA) Verispan's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

¹² DuMouchel W, Pregibon D. Empirical bayes screening for multi-item associations. Proceedings of the conference on knowledge discovery and data; 2001 Aug 26-9; San Diego, Ca: ACM Press:67-76.

¹³ Szarfman A, Machado SG, O'Neill RT. Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. Drug Safety 2002;25:381-92.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 1.5 billion prescription claims per year, representing over 100 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients. Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. Verispan receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

Verispan, LLC: Vector One®: Total Patient Tracker (TPT)

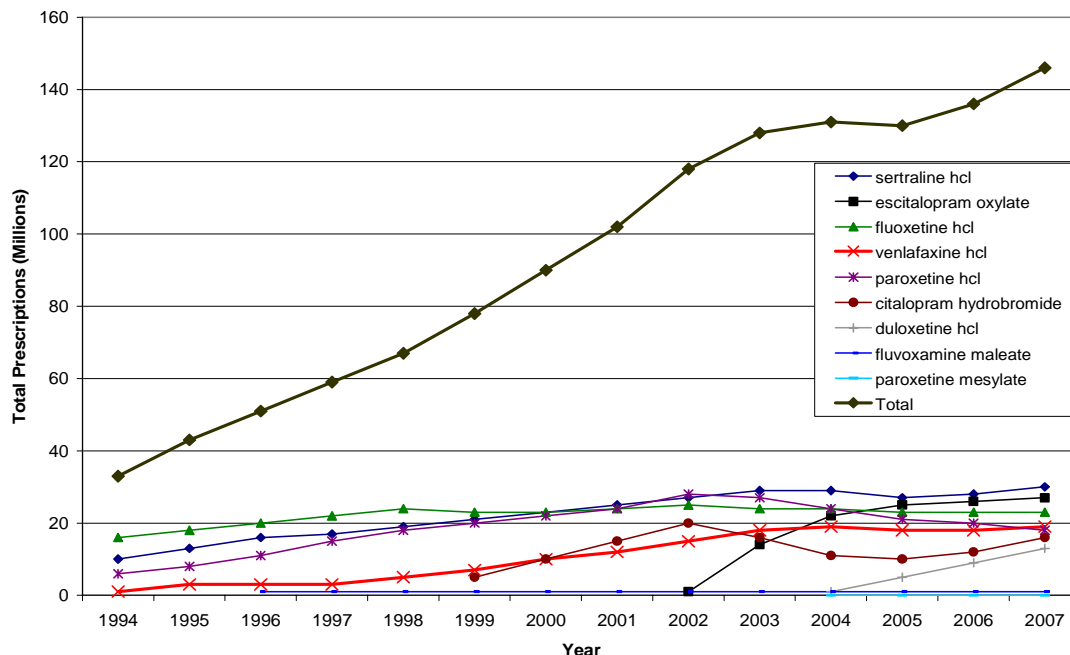
Verispan's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers, and their data systems. Vector One® receives over 2 billion prescription claims per year, which represents over 160 million patients tracked across time.

8.5

DRUG USE

Total Prescriptions by Year 1994 to 2007



Source: Verispan, LLC. Vector One: National, Years 1994 – 2007. Extracted Feb 08, file: venlafaxine vs. other SNRIs and SSRIs.xls.

THE USE OF THE WHO-UMC SYSTEM FOR STANDARDISED CASE CAUSALITY ASSESSMENT

Causality term	Assessment criteria*
Certain	Event or laboratory test abnormality, with plausible time relationship to drug intake Cannot be explained by disease or other drugs Response to withdrawal plausible (pharmacologically, pathologically) Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) Rechallenge satisfactory, if necessary
Probable / Likely	Event or laboratory test abnormality, with reasonable time relationship to drug intake Unlikely to be attributed to disease or other drugs Response to withdrawal clinically reasonable Rechallenge not required
Possible	Event or laboratory test abnormality, with reasonable time relationship to drug intake Could also be explained by disease or other drugs Information on drug withdrawal may be lacking or unclear
Unlikely	Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) Disease or other drugs provide plausible explanations
Conditional / Unclassified	Event or laboratory test abnormality More data for proper assessment needed, or Additional data under examination
Unassessable / Unclassifiable	Report suggesting an adverse reaction Cannot be judged because information is insufficient or contradictory Data cannot be supplemented or verified

PUBLISHED LITERATURE CASE REPORTS FROM DPP REVIEW

Dubitsky, G. Review and Evaluation of Clinical Data, NDA #20-151, 07/12/06

The index case in this Annual Report was described by Pradeep and colleagues in the Journal of the Association of Physicians of India:

• a 30 year old depressed male with no significant medical or alcohol abuse history was started on venlafaxine 37.5 mg/day. Over the next four months, the dose was gradually increased to 150 mg/day then continued for about six months. At that time, he presented with a 15 day history of generalized weakness, nausea, and vomiting. Laboratory assays revealed a increased AST (167 U/L, ULN=37), ALT (81 U/L, ULN=65), GGT (677 U/L, ULN=50), and conjugated bilirubin (0.5 mg/dl, ULN 0.04); total bilirubin was slightly increased (1.1 mg/dl, ULN=1.0). Other causes of hepatotoxicity were ruled out, including B and C viral hepatitis and HIV. An abdominal ultrasound was normal. Venlafaxine was tapered and dothiepin was started. A week later, the patient was clinically improved and repeat liver function tests were significantly improved (GGT 148 U/L).

Pradeep RJ, et al. Venlafaxine Induced Hepatitis. JAPI 2004;52:340.

Horsmans and colleagues describe a 44 year old woman who was treated with venlafaxine for depression and had normal liver function tests at the time venlafaxine was begun. She had also been taking lorazepam and trazodone for several months. After about six months of treatment, she complained of severe asthenia and liver transaminases were found to be elevated: AST 661 U/L (normal <40) and ALT 1082 U/L (normal <56). Results of serologic tests were normal or negative and abdominal ultrasound showed no abnormalities. A percutaneous liver biopsy revealed well demarcated acinar zone 3 confluent necrosis with some inflammation and clumps of perivenular Kupffer cells containing lipid-rich ceroid pigment. Histologic findings were deemed to support drug-induced hepatotoxicity. Portal tracts were not affected. Venlafaxine was gradually tapered and liver function tests returned to normal four months after discontinuing venlafaxine. Lorazepam and trazodone were continued.

Horsmans Y, et al. Venlafaxine-Associated Hepatitis [letter]. Ann Int Med 1999;130(11):944.

Cardona and coworkers describe a 78 year old male with a major depressive episode who had been treated with ECT two months before admission. He began venlafaxine therapy 37.5 mg/day, which was increased to 150 mg/day about one month later. Six days after the dose increase, he was admitted with acute icteric hepatitis and the following laboratory abnormalities were noted: ALT 3.97 μ kat/L (normal <1.08), AST 4.36 μ kat/L (normal <0.62), GGT 12.17 μ kat/L (normal <1.42), alkaline phosphatase 11.33 μ kat/L (normal <2.27), total bilirubin 87 μ mol/L (normal <17.1), and direct bilirubin 86 μ mol/L (normal <5.5). Previous liver function tests were normal. Serologic tests for hepatitis A, B, and C were negative and abdominal ultrasound showed no abnormalities. Venlafaxine was gradually tapered and his condition improved, with liver function tests returning to normal within five weeks. Medical history was remarkable for Parkinson's disease, which was treated with levodopa and pergolide throughout the episode.

Cardona X, et al. Venlafaxine-Associated Hepatitis. Ann Int Med 2000;132(5):417.

Sencan and colleagues report a case of hepatitis associated with venlafaxine in a patient chronic hepatitis B. A 30 year old woman was admitted with complaints of weakness and nausea six weeks after beginning treatment with venlafaxine 37.5 mg/day for depression. Liver transaminases were significantly elevated: AST 369 U/L (normal 0-38) and ALT 689 U/L (0-41). Over the prior year, liver enzymes had been increased to about twice the upper limit of normal secondary to chronic hepatitis B. She had completed a course of alpha interferon two months before admission and, at that time, both AST and ALT were within normal limits and serologic tests for hepatitis B, hepatitis C, hepatitis D, and DNA polymerase chain reaction were negative. On admission, serologic tests were unremarkable, abdominal ultrasound was normal, and no history of hepatotoxic drug or alcohol intake was reported. Discontinuation of venlafaxine led to clinical and laboratory recovery.

Sencan I, et al. Low-dose venlafaxine-associated liver toxicity in chronic hepatitis. Ann Pharmacother 2004;38:352.

Phillips and coworkers published a report of a 60 year old woman who was treated with venlafaxine 75 mg/day for one month for postmenopausal vasomotor symptoms. At that time, she presented with nonspecific complaints, including right upper quadrant abdominal pain. Workup revealed an enlarged liver on ultrasound and markedly elevated liver functions tests: ALT 372 U/L (normal 0-20), AST 99 U/L (normal 0-31), and alkaline phosphatase 483 U/L (normal 35-104); GGT two days later was also substantially increased (962 U/L, normal 5-36). Laboratory tests, including hepatitis serologies, were negative. Alcohol use was reported as one glass of beer or wine, three or four times per week prior to symptom onset. Concomitant medications included acetaminophen 1,000mg tid. Venlafaxine and other medication possibly related to hepatotoxicity were stopped.

and, within one week, liver function tests and clinical symptoms were significantly improved. Four weeks after discontinuing venlafaxine, it was restarted at a dose of 37.5 mg/day. Five days after resuming venlafaxine therapy, her transaminase levels were again elevated (ALT 269, AST 49, GGT 256, and alkaline phosphatase 263 U/L). Alcohol consumption and acetaminophen use were not resumed during this rechallenge with venlafaxine. Liver function abnormalities returned to near baseline levels two weeks after discontinuing venlafaxine. This case is remarkable given the association of hepatitis with low dose venlafaxine and the positive rechallenge.

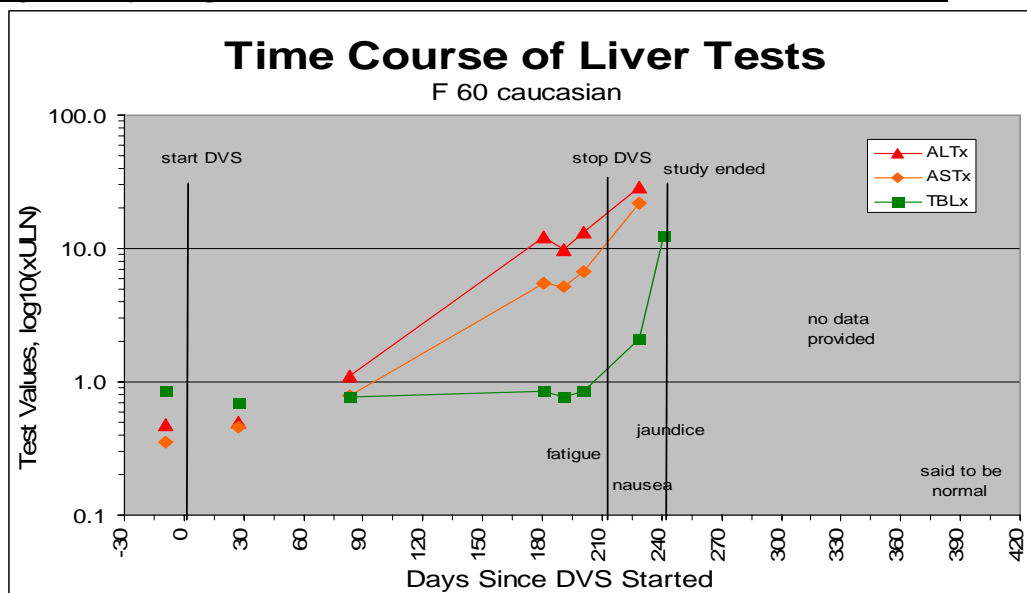
Phillips BB, et al. Hepatitis Associated with Low-Dose Venlafaxine for Postmenopausal Vasomotor Symptoms. Ann Pharmacother 2006;40:323-7.

EXCERPT FROM OSE REVIEW - POSSIBLE HEPATOTOXICITY AND DESVENLAFAXINE

Senior, J. 2007, Office of Surveillance and Epidemiology, Memorandum, Possible hepatotoxicity of desvenlafaxine (PRISTIQ, Wyeth), 03/28/07.

The most compelling of the cases appeared to be that of study participant 315-206-201251, a 60-year-old white woman weighing 89.5 kg, 1.65 m tall (body mass index, BMI, 32.9, in the obese range). She had a history of long-term obesity, and had been taking Macrobid (nitrofurantoin) since 2002 until 24 March 2004 (or ? 13 September) for repeated urinary tract infections. Her case report also listed ganglion cyst treated in 1962, cholecystectomy and hepatitis (unspecified) in 1971, low back pain 2001, and arthritis 2003. She took also a variety of dietary supplements, including garlic, cranberry concentrate, Ginkgo biloba, soy bran, vitamin E and multivitamins, and Advair discus. She was screened for study 315 on 8 January 2004, then was randomized to DVS SR 150 mg on (b) (6) and continued medication until (b) (6) (214 days, or more than 30 weeks, according to the narrative summary, which was corrected from the case report). During the study she had a urethral sling procedure on (b) (6) after which she took Vicodin that day and the following day for pain relief. Her ALT and AST were noted to be high on (b) (6) after 182 days of DVS treatment, confirmed to be high on (b) (6). The drug was stopped on (b) (6) after 214 days of treatment. She was diagnosed as having "cholestatic hepatitis" on (b) (6), and a hepatitis panel was reported to be taken that day. She was removed from the study on (b) (6) and was followed by the company until (b) (6), but none of the findings were reported in detail in the narrative. The narrative states she was never hospitalized, but a note from a study monitor said she was. The data for the patient reported in the narrative are shown below:

Figure 1. Study Participant 315-206-201251, Desvenlafaxine Clinical Trial, NDA 21966 (Senior 03/28/07)



Comment The course of this woman's liver test abnormalities suggests onset of hepatocellular injury sometime between April and July 2004, not better defined because she was not tested in between. No alkaline phosphatase results were reported, and the bilirubin did not rise until after the drug was stopped. She was removed from the study, and although many tests were done, a diagnosis of "cholestatic hepatitis" was made, and she was followed for another 6 months, no data were reported in this submission. There is no clear justification for the diagnosis, which appears more like acute hepatocellular injury, onset about 4 months after initial exposure to the drug, with jaundice following discontinuation of the DVS in mid-August, fulfilling criteria for a "Hy's Law" case, or one that is potentially serious and may indicate that other patients may have worse outcomes if exposed to the drug. The records in the case report and narrative are conflicting as to whether she was hospitalized or not, but no data are provided. The case report is also conflicting on when the nitrofurantoin was stopped 24 March or 2 September 2004. In short, this case may be an important indicator of possible serious hepatotoxicity risk from this drug, rare but potentially severe, and more likely to occur after prolonged administration of the drug, rather than in the first few weeks.

The sponsor's reliance on group means for detection of laboratory test abnormalities tends to obscure rather than detect individual cases that are relatively uncommon or rare. It would be better to look for individual cases of enzyme elevations, especially those associated with rises in serum bilirubin or plasma prothrombin time that occur with or following the enzyme increases, as indications of truly impaired functions of the liver (which aminotransferases are not). When such cases are found, complete display of all data over the course of administration of the drug and afterward until normalization of all findings should be done.

The general tenor of the sponsor's report of study 315 was to downplay or minimize the findings for possible hepatotoxicity of the drug, even though there had been cases reported in the literature of some fairly serious venlafaxine-induced liver injury. The O-desmethyl derivative of venlafaxine is pharmacologically active, and now being studied for the current indications as DVS. If used for months or longer, effects that did not appear after short-term use might become evident, as seen with some other drugs (fialuridine, bromfenac, trofloxacin, ximelagatran).

Comment There is no way to predict whether DVS will show only the occasional serious liver toxicity of venlafaxine, or whether the O-desmethyl derivative will be safer than the parent compound. The incidence of venlafaxine-induced liver injury was not great enough to lead to labeling precautions or warnings, but it seems prudent to be on the lookout for hepatotoxicity induced by DVS. Here we one case that fulfills "Hy's Law" criteria, a woman who recovered after the drug was withdrawn, slowly over several months. The sponsor apparently did not consider this case a serious adverse event but it should have been, and full data should have been reported in the safety summary. None of the other five cases mentioned here were particularly alarming, but are worth noting, and probably would show an incidence greater than in those on placebo. If the short-term studies were negative for hepatotoxicity of DVS in the depression studies (NDA 21-992), then perhaps we may have another instance of a drug that can have a prolonged latent period after beginning of exposure until first evidence of liver injury, as seen previously with drugs such as fialuridine, bromfenac, trofloxacin, and ximelagatran that were tolerated for short-term administration of 2-4 weeks, but on longer exposure produced cases of severe liver injury.

8.9 VENLAFAXINE CASE SERIES – OSE 2006-410

* if normal range not reported, 40 U/L used for ALT **if normal range not reported, 100 U/L used for ALP ULN, SLI – serious liver injury

ISR #	Time to onset	Peak ALT*	peak AST	Peak bili	Peak ALP**	Type of acute liver injury	Virals	Auto-immune	Biopsy/histology/cause of death (COD)	Concomitant drugs	Association	Primary reported outcome
1674195	5	not reported (nr)	nr	nr	nr	nr	hep a ig +	neg	nr	tylenol/methotrexate/feldene/terfenadine/prilosec	Possible - also taking methotrexate and feldene - no dates provided - BS 2 on admission - urine screen + for tricyclic	DE
1851877	dose increase - approx 2 months to abdominal pain/jaundice -3 months to admit	174 (uln 55)	978 (uln 38)	224 (ULN 22)	295 (uln 125)	onset ALT 119, ALP 295, Tbili 82, Dbili 59 Ratio .91 cholestatic	neg	neg	drug induced - acute hepatic necrosis with minimal cholestasis, ? Of underlying cirrhosis	1995 zopiclone, clonazepam, 03/05/96 clozapine, 02/96 venlafaxine - dose increased from 37.5 -225	Possible - more temporal with clozapine - dose increase dates not reported	HO
3153379	54, DOSE INCREASE 4-5 wks pta	6000	nr	5.0	nr	ALP nr	nr	nr	COD hepatic failure	tylenol, atenolol, amlodipine, acarbose, glyburide, diazepam, warfarin 07/98, ASA, pravastatin, venlafaxine 37.5 07/14 - increased to 75mg-8/??/98	Possible - report includes conflicting information regarding etiology - possibly allergic reaction to penicillin and erythromycin	DE
3160091	dose increase 15 days PTA, 369 days	47.3 (uln 0.7)	33.1 (uln 0.7)	152 (uln 20)	8.1 (uln 5)	onset ALT 47.3, ALP 8.1, Tbili152, Ratio 41.7 hepatocellular	nr	nr	only signs compatible with drug toxicity - COD unsuccessful liver transplant - renal insufficiency, hepatic and circulatory collapse	tylenol 1500-2gms/day > 1yr, fupenthixol 01/96, naproxen >1yr, alprazolam 1988, propiomazine 1993, venlafaxine 75mg 09/13/96 titrated up to 300mg/day by 07/23/97, SLI 09/25	Possible - also apap/naproxen - death after unsuccessful liver transplant	DE
3693573	53 days to onset of dark urine/ 60 to SLI	nr	nr	nr	nr	nr	nr	nr	nr	unspecified bronchodilators and inhalers for COPD	Possible/likely - clay colored stools, dark patches on skin, dark urine 1wk PTA, ETOH 15 years PTA, none recent	HO

ISR #	Time to onset	Peak ALT*	peak AST	Peak bili	Peak ALP**	Type of acute liver injury	Virals	Auto-immune	Biopsy/histology/cause of death (COD)	Concomitant drugs	Association	Primary reported outcome
3725126	22 days	4XN	50XN	141T	nr	ALP nr	nr	nr	COD - fulminant hepatitis d/t decompensated cirrhosis that might have been caused by drug toxicity, then hepatic ischemia during sepsis and hemorrhagic shock	oxazepam/disulfuram/cyamemazine	Possible - chronic ETOH/fatty liver - transaminase profile more consistent with ETOH	DE
3826334	63 days	1490	nr	36	120	onset ALT 1242, AP, 106, Bili 20 Ratio 29.8 hepatocellular	nr	nr	COD - hepatic failure	07/21-08/07 tylenol 4gm/day, 07/22-23 cefuroxime peri-op 2 doses, 06/21-08/15 venlafaxine, 08/15 SLI, hemiarthroplasty 07/22 or 23	Possible - APAP possible, cefuroxime unlikely - not temporal, 2 doses only, 2 weeks s/p hip surgery	DE
3974045	nr	nr	nr	nr	nr	nr	nr	nr	acute liver necrosis involving 1/4 of parenchyma - COD acute liver necrosis and CAD	nr	Possible - no dates/concomitants/history reported, no dx for punctate pustular rash, possible sepsis	DE
3978675	unwell for 3 weeks, SLI 23 days	nr	nr	nr	nr	nr	nr	nr	severe zone 3 necrosis, no features of etoh liver disease	terbutaline long term, 06/01 venlafaxine 06/23 SLI	Possible/likely - positive dechallenge - ETOH 60 units/week	DE
4011014	27 days	1094 (uln 24)	1046 (uln 34)	10 (24 ULN)	1815 (ULN 127)	onset ALT 1094, ALP 567, bili 10 Ratio 10.22 hepatocellular	nr	nr	nr	ASA, metoprolol, venlafaxine 10/4, quetiapine 10/29, ALF 10/30	Possible - temporal with seroquel not labeled for hepatitis	HO
4111928	nr	nr	nr	nr	nr	nr	nr	nr	COD - primary - hepatorenal syndrome, secondary myocardial ischemia	bisoprolol, digoxin, furosemide, sorbitol, ranitidine, clopidogrel	Possible - leukocytoclastic vasculitis 03/18 - not in organs	DE
4301605	on 150 for "over a month"	nr	nr	nr	nr	nr	nr	nr	COD - fulminant hepatitis	nr	Possible - concomitants nr	DE

ISR #	Time to onset	Peak ALT*	peak AST	Peak bili	Peak ALP**	Type of acute liver injury	Virals	Auto-immune	Biopsy/histology/cause of death (COD)	Concomitant drugs	Association	Primary reported outcome
4314537	43, dose increase 33 days pta	1950	1190	611T	nr	ALP nr	neg	igg+, igm-	cholestasis	mirtazapine 06/02, valproate 10/17/03, venlafaxine 10/27/03, oxazepam no dates, SLI 12/13	Possible - valproic - cholestasis - hx of jaundice with mirtazapine, ETOH in past, possible hep as a child	HO
4382206	12 DAYS	678 12/22 - 234	717 12/22 - 39	38.6 12/22 - 0.5	377 12/22 - 115	onset ALT 545, ALP 377, Tbili 26.8, Ratio 3.57 mixed	nr	nr	nr	HCTZ ??, lansoprazole 12/22, montelukast - labeled for hepatitis 12/17?22, amlodipine labeled for cholestasis/hepatitis12/19?31 mirtazapine 12/29?31, venlafaxine 12/29?31, SLI 01/12/04	Possible - conflicting info - ? labs increased before venlafaxine, also mirtazapine	DE
4536028	6 days	8000s	nr	4.5		ALP nr	neg	neg	drug induced - mod-sev inflammation with lump, neut and eos. Severe piecemeal necrosis with periportal dropout. Mod-sev steatosis.	no concomitants, 08/10 venlafaxine, SLI 08/16	Probable - no confounding, no concomitants, no comorbid conditions	HO
4762171	46 days elevated LFTs, 76 days SLI	14704	20987	2.8	213	onset ALT 14704, ALP 213, bili 2.8, Ratio 172.6 hepatocellular	nr	nr	nr	tylenol 5.0, provigil , fluoxetine , alprazolam	Possible - also apap - ?increased WBC, decreased plt, ETOH	HO
4932274	nr	703.4	415	25 - T	181	onset ALT 703.4, ALP 181, bili 21.08 Ratio 9.78 hepatocellular	nr	nr	nr	butyrophenone and venlafaxine July-Oct	Possible - cholestatic hepatitis with melperone - 2nd hospitalization for SLI - 1st time in November, Dc 1203 with declining alt and bili of 25, readmitted on 12/05	HO
5220627	48 days _ 30days - n/v	3662 (uln 31)	2289 (uln 31)	345 T (uln- <20n)	141 (uln 100)	onset ALT 3662, ALP 141, Tbili 345, Ratio 84.3 hepatocellular	neg	neg	drug induced	12/02-19 lorazepam, 12/05 venlafaxine, SLI 01/25	Possible - no resolution after dc	HO
5220835	1994 days	nr	nr	nr	nr	nr	nr	nr	nr	diabetes, hepatic coma, jaundice, venlafaxine level 3259 increased 3X	Possible -increased serum level and CYP450 problem - possible role for ETOH d/t time to onset	HO

ISR #	Time to onset	Peak ALT*	peak AST	Peak bili	Peak ALP**	Type of acute liver injury	Virals	Auto-immune	Biopsy/histology/cause of death (COD)	Concomitant drugs	Association	Primary reported outcome
5306313	4 days	7000	23000	89	97	onset ALT 7000, ALP 97, bili 89 Ratio 180.4 hepatocellular	nr	nr	COD - fulminant hepatitis	01/09 tylenol/tramadol - 01/12 venlafaxine, 01/19 ALF	Possible - apap also, aggravated renal failure and afib noted to prolong hospitalization	DE
5470782	33 days	65.4XN	80.7XN	23.4T/9.3C	nr	alp nr	nr	nr	nr	dig toxic (1 9), K+ 5.6, amlodipine, ASA, alprazolam, amitriptyline, risperidone - all long term - venlafaxine 6/14, amoxicillin 08/13, ALF 08/18	Possible - more temporal with amoxicillin - well 2-3 days PTA - also dig toxic, hx of mod renal failure	DE

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: September 18, 2007

To: Thomas Laughren, Director,
Division of Psychiatric Products (DPP)

Thru: Dr. Mark Avigan, Director,
Division of Drug Risk Evaluation (DDRE)

From: Jenna Lyndly, R.N., Safety Evaluator
Division of Drug Risk Evaluation (DDRE)

Subject: Bleeding; NME Review Follow-up

Drug Name(s): Duloxetine (Cymbalta)

Application Type/Number: 21-427, 21-733

Applicant/sponsor: Lilly

OSE RCM #: 2007-1096

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EXECUTIVE SUMMARY

The objective of this review is to analyze post-marketing data concerning duloxetine and bleeding events, and is being performed as follow-up suggested by the Duloxetine NME Review team that met on March 13, 2007¹.

Duloxetine is a serotonin-norepinephrine reuptake inhibitor approved to treat major depressive disorders, diabetic peripheral neuropathic pain and generalized anxiety disorders. OSE retrieved and analyzed 170 unique post-marketing cases with reports of bleeding during duloxetine therapy. While GI system bleeding was the most frequently reported location of bleeding, bleeding was also reported in locations throughout the body and ranged in severity from bruising to a fatal GI hemorrhage. Six reports of death were included in the case series. Four² of the deaths were unrelated to duloxetine; however, a role for duloxetine cannot be excluded in two of the deaths.³ In addition, 33 of 51 hospitalizations were reportedly due to the bleeding event, with one death and 12 hospitalizations concomitantly using anti-coagulants, ASA and/or NSAIDs. The cases series included reports of platelet dysfunction, thrombocytopenia and increased PT/INR results associated with duloxetine therapy. Sixty positive dechallenges were described, but most compelling were the four positive rechallenges.

The duloxetine case series and the current literature are supportive of an increased risk of bleeding with drugs that inhibit serotonin, particularly in those patients using ASA, anticoagulants and/or NSAIDs. The literature has urged health care providers to use caution when prescribing a drug that inhibits serotonin to patients of advanced age, patients with a medical condition which might affect hemostasis and patients concomitantly using drugs which affect hemostasis. An increased risk may also be present for patients with an underlying hemostatic defect, either a coagulation defect or a platelet dysfunction. As of December 2006, over 3 million patients were prescribed duloxetine. Adding language similar to the SSRIs (see 1.3 Product Labeling) to the Precautions, Drug Interactions and Patient Information sections in both SNRI labels, duloxetine and venlafaxine, will alert the practicing community and patients to potential bleeding complications with SNRI therapy.

Therefore, OSE recommends:

- 1 Consider adding the precaution for “abnormal bleeding” found in the SSRI labels to the SNRI (duloxetine and venlafaxine) labels. Also consider adding language describing duloxetine associated thrombocytopenia or platelet dysfunction.
- 2 Consider adding the drug interaction language for warfarin and drugs that affect hemostasis (ASA, NSAIDs and anticoagulants) found in the SSRI labels to the SNRI labels.
- 3 Consider adding patient information language regarding concomitant use of ASA, NSAIDs or anticoagulants found in the SSRI labels to the SNRI labels.

¹ New Molecular Entity (NME) Postmarketing Evaluation, NDA 21-427, March 13, 2007

² ISR # 4540780 – decompensated heart insufficiency with lung edema, ISR # 5260807 – central pontine myelinosis due to rapid sodium level correction, ISR # 5159352 – accidental death due to multiple drug intoxication, ISR # 4860668 – congestive heart failure

³ ISR #4674574 – cerebral hemorrhage, ISR # 4800401 – cardiac arrest secondary to hypovolemic shock secondary to GI hemorrhage

BACKGROUND

1.1 INTRODUCTION

The FDA is piloting a regularly intervalled review process for drugs classified as new molecular entities⁴ (NME). Duloxetine was selected as the first drug product to undergo the NME review process. On March 13, 2007, OND and OSE brought together a multidisciplinary team to review the safety profile of duloxetine since its approval in August of 2004. The review process identified potential bleeding disorders as a DPP concern and also a topic of ongoing surveillance by the sponsor.

DDRE reviewed SSRI⁵ post-marketing adverse event reports for bleeding in 2000 concluding SSRI use “may contribute to an increased risk of bleeding in various body systems” which “may be associated with serious outcomes including death or disability.”⁶ The review recommended that all SSRIs have labeling regarding a potential risk for increased bleeding. In 2003, OND determined there was sufficient evidence of increased bleeding risk associated with use of SSRIs and requested class labeling.⁷

Duloxetine is an inhibitor of serotonin reuptake, providing biological plausibility for a concern of potential increased bleeding risk with use of duloxetine. As a result of this concern, the multidisciplinary review team recommended an analysis of duloxetine post-marketing reports of bleeding, which this analysis provides.

1.2 REGULATORY HISTORY

Duloxetine is classified as a serotonin-norepinephrine reuptake inhibitor (SNRI), and was originally approved in the US on August 3, 2004 as Cymbalta™ to treat major depressive disorders. Cymbalta™ was approved to treat diabetic peripheral neuropathic pain on September 3, 2004 and generalized anxiety disorder on February 23, 2007. Duloxetine is available in 20mg, 30mg and 60mg doses

1.3 PRODUCT LABELING⁸

The current duloxetine labeling addresses some specific events related to bleeding in the Adverse Reactions section.

In the “Other Adverse Events Observed During the Premarketing and Postmarketing Clinical Trial Evaluation of Duloxetine” section:

Gastrointestinal Disorders – Rare: hematochezia, melena.

⁴ A new molecular entity (NME) means a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act.

⁵ SSRI – selective serotonin reuptake inhibitor

⁶ Phelan, Kathleen. OPDRA Postmarketing Safety Review, Hemorrhages with Serious Outcomes, May 8, 2000

⁷ Hughes, Alice and Judith Racoosin, Review and Evaluation of Clinical Data, November 19, 2003

⁸ Drugs@FDA, Cymbalta, NDA 021427, label approved on 02/23/2007

Skin and Subcutaneous Tissue Disorders – Infrequent: increased tendency to bruise;
Rare: ecchymosis.
Blood and Lymphatic System Disorders — Infrequent: anemia; Rare: leukopenia and
thrombocytopenia.

In the “Drug-Drug Interactions” section:

Drugs Highly Bound to Plasma Protein — Because duloxetine is highly bound to plasma protein, administration of Cymbalta to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse events.

The SSRIs include class labeling in the Precautions section addressing the potential for increased bleeding. (See below):

General⁹

Abnormal Bleeding — Published case reports have documented the occurrence of bleeding Episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In two studies, concurrent use of a nonsteroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding (*see* DRUG INTERACTIONS). Although these studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of Prozac with NSAIDs, aspirin, or other drugs that affect coagulation.

In addition, the SSRI labels include similar to the Prozac¹⁰ labeling shown below:

In the Information for Patients section:

Patients should be cautioned about the concomitant use of fluoxetine and NSAIDs, aspirin, or other drugs that affect coagulation since combined use of psychotropic drugs that interfere with serotonin reuptake and these agents have been associated with an increased risk of bleeding.

In the Drug Interactions section:

Drugs that interfere with hemostasis (NSAIDs, aspirin, warfarin, etc.) — Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin

⁹ NDA 18936, Prozac label approved 08/02/07, Drugs@FDA

¹⁰ NDA 18936, Prozac label approved 08/02/07, Drugs@FDA

potentiated the risk of bleeding. Thus, patients should be cautioned about the use of such drugs concurrently with fluoxetine.

Warfarin — Altered anticoagulant effects, including increased bleeding, have been reported when fluoxetine is coadministered with warfarin. Patients receiving warfarin therapy should receive careful coagulation monitoring when fluoxetine is initiated or stopped.

2 METHODS AND MATERIALS

2.1 INTRODUCTION

We utilized adverse event reports retrieved from the AERS database, drug use information from Verispan¹¹ and an analysis of the AERS database by WebVDME¹² (data mining) as data sources for this review.

2.2 DATA MINING

We utilized data mining, which scores drug-event combinations based on disproportional analysis comparing a drug-event against the AERS database. Because AERS is a spontaneous adverse events reporting system and confounding is not evaluated prior to inclusion in the database, the actual risk for a drug-event cannot be determined from data mining. Data mining provides a signal which must be further investigated. The absence of an elevated EB05 score for a drug-event cannot be interpreted as a definite lack of toxicity for that drug-event or the absence of a signal. Eli Lilly, the sponsor of duloxetine, was granted a waiver for non-serious labeled adverse events on February 7, 2005¹³; therefore, non-serious, labeled adverse events may be under-represented in the data mining analysis. Additional information concerning data mining as a surveillance tool is included in Appendix 1.

“We queried WebVDME on January 3, 2007 for duloxetine and adverse events with an EB05 score of 2.0 or greater.”¹⁴

2.3 LITERATURE SEARCH

On July 9, 2007, we queried PubMed Central with the terms “duloxetine and bleeding”, “duloxetine and hemorrhage”, “duloxetine and coagulation”, “duloxetine and purpura”, “duloxetine and thrombocytopenia”, “SNRI and bleeding”, “serotonin and norepinephrine reuptake inhibitor and bleeding”, “serotonin and bleeding”, “venlafaxine and bleeding” and “serotonin and coagulation”. Titles and selected abstracts were reviewed in all search results to identify relevant case reports of bleeding disorders associated with duloxetine and/or SNRIs.

¹¹ Verispan, LLC: Total Patient Tracker, Aug04-Dec06, Extracted Feb07. Files: TPT Cymbalta AUG04-DEC06 Aggregate Product Brand Report.xls, TPT Cymbalta aug04-dec06 Aggregate Gender Report.xls

¹² Developed by Lincoln Technologies, Inc. in cooperation with the FDA

¹³ The non-serious labeled reports of bleeding are most likely under-represented in the AERS database, and consequently under-represented in WebVDME.

¹⁴ OSE Post-Marketing Data Mining Analysis, February 20, 2007, Marilyn Pitts

2.4 AERS SELECTION OF CASES

We queried the AERS database as follows:

Table 1: AERS Search Strategy

Date of Search:	April 26, 2007
Drug Name Search Terms:	Duloxetine active ingredient and related verbatim terms
MedDRA Adverse Event Search Terms:	Standardized MedDRA Query (SMQ) “Haemorrhage terms (excl laboratory terms)”
Search Level:	Preferred Terms (PT)

A description of the AERS database and a listing of the preferred terms included in the Haemorrhage SMQ are provided in Appendix 2.

2.5 DRUG USE DATA

We utilized drug use data obtained by the Division of Surveillance, Research and Communication Support (DSRCS) provided during the March 13, 2007 NME review for duloxetine. DSRCS obtained prescription volume data and patient gender data from Verispan, LLC. A description of the Verispan database is provided in Appendix 3.

3 RESULTS

3.1 DATA MINING

The January 3, 2007 query did not identify any preferred terms related to bleeding with an EB05 score of 2.0 or greater.

3.2 LITERATURE SEARCH

The literature includes a large number of articles related to bleeding and SSRIs and/or serotonin. To provide an overview, four recent reviews were identified with the search terms “serotonin and bleeding”. One relevant article from each of the search terms “duloxetine and coagulation” and “duloxetine and bleeding” was identified. An abstract from an article not available in English and two articles were located with the search terms “venlafaxine and bleeding”.

Serotonin Inhibition and Bleeding

Four current reviews, two published in 2007 and two in 2006 were identified to provide an overview of the role of the current knowledge regarding serotonin inhibition in bleeding. Turner et al. (2007) reviewed literature from 1966 to May 2006 including case reports and nine observational studies. They noted that multiple theories have been proposed for the potential mechanism of action for increased bleeding with SSRI use including blockade of calcium mobilization, inhibition of nitric oxide “synthase”, decreased platelet secretion in response to

collagen, decreased platelet binding affinity and decreased serotonin in platelets.¹⁵ Six of the nine studies reviewed showed an increased risk of bleeding with SSRI use. Turner et al. noted that an increased risk of bleeding was seen with SSRIs and ASA/or NSAIDs which exceeded the additive effect of the medications.

Halperin and Reber (2007) reviewed published case studies, epidemiological studies and prospective studies with a focus on studies with laboratory values for anti-depressant use and hemostasis. Retrospective studies reviewed by Halperin and Reber supported a causal association between abnormal bleeding and antidepressants, especially the SSRIs. While the prospective studies they reviewed had conflicting results, they concluded the studies “clearly indicate that anti-depressants modify primary hemostasis.”¹⁶ Decreased platelet aggregability and activity, and prolonged bleeding time were the two most frequently altered primary hemostasis laboratory values in the data reviewed. However, about 50% of the case reports reviewed by Halperin and Reber had normal hemostasis markers, which they indicated was an expected result, as the majority of hemostasis laboratory values have a low sensitivity. They noted that platelet aggregation tests show the highest sensitivity but are not routinely performed.¹⁷

SSRI and upper gastrointestinal (UGI) bleeding were the topics of a search from 1980 to May of 2005 used by Yuan et al. (2006) to identify observational and interventional studies for their review. They noted that multiple mechanisms of actions have been proposed, but one mechanism has not been clearly identified. The currently purported mechanism was described as a “decrease in platelet serotonin leading to a defect in platelet aggregation, resulting in an impairment of hemostatic function leading to a prolonged bleeding time and abnormal platelet count.”¹⁸ While Yuan et al. noted that the evidence provides “weak support” for an increased risk of UGI bleeding with SSRI use in most patients, the literature does support an increased risk of UGI bleeding in patients using NSAIDs, ASA and/or anticoagulants, patients with a history of GI bleeding or elderly patients. They advised caution when using SSRIs in patients concomitantly using NSAIDs/aspirin who have a risk of increased bleeding as the literature includes a case of a fatal GI bleed in a patient with cirrhosis using paroxetine and aspirin. In addition, they expressed a concern due to increased use of SSRIs in the elderly who frequently have pre-existing medical conditions which may increase their risk for UGI bleeding and are on aspirin/NSAIDs.

Serebruany (2006) noted that while there is a preponderance of literature (120 Medline papers and more than 50,000 web pages) related to SSRIs and bleeding, there is no reliable incidence for bleeding events; however, he indicated that the “anecdotal evidence is alarming”. He notes there is a “strong consensus that blockade of serotonin reuptake affects primary hemostasis.”¹⁹, and concludes serotonin platelet and plasma levels most likely impact an array of factors during primary hemostasis. Serebruany highlighted the fact that all SSRIs have been associated with bleeding as well as antidepressants with partial serotonin inhibition such as venlafaxine.

Duloxetine and Bleeding

¹⁵ Turner et al., page 206-7.

¹⁶ Halperin and Reber, page 56

¹⁷ Halperin and Reber, page 56

¹⁸ Yuan et al., page 719

¹⁹ Serebruany, page 114

The literature search for ‘duloxetine and bleeding’, and ‘duloxetine and coagulation’ resulted in two case reports. Glueck et al. described a patient, previously stable on warfarin, with an increased INR after initiation of duloxetine therapy, with the elevation continuing after warfarin was discontinued, and remaining elevated until duloxetine was discontinued. The patient’s INR then returned to the normal range. Warfarin was restarted and the patient’s INR remained stable and within the expected range. Balhara et al. described a case of bleeding with duloxetine and noted that the patient had not had a similar reaction to fluoxetine, escitalopram or amitriptyline. When given duloxetine, his gums became raw and oozed blood from the surface. No alternative cause of bleeding could be identified and coagulation tests were within normal limits. The bleeding resolved within one week of discontinuing duloxetine. Balhara et al. propose that the mechanism for duloxetine bleeding events may differ from the SSRIs, as the patient did not experience bleeding events with SSRIs.

Venlafaxine and Bleeding

Three case reports were identified in the literature for venlafaxine and bleeding. Horne et al. described a case report of positive dechallenge and positive rechallenge with venlafaxine resulting in generalized bruising. The patient’s coagulation tests were normal with the exception of a prolonged bleeding time 8.5 at the initial presentation of bruising. Platelet aggregation studies were performed prior to the rechallenge and were normal but both platelet aggregation and ATP release were markedly depressed after the second presentation of generalized bruising. A second case report was detailed by Linnebur et al. which described post-menopausal bleeding with venlafaxine including a positive dechallenge and positive rechallenge response. An abstract by Chakarian et al. reported onset of abdominal pain with subsequent identification of a splenic hematoma in a patient with no recent injuries while on venlafaxine therapy.

Disorders of Hemostasis

Harrison’s²⁰ notes that patterns of bleeding are associated with different types of coagulation disorders. Bleeding into the joints, muscles and body cavities hours or days after an injury is indicative of the congenital coagulation defects which result in a prolonged PT and/or PTT. Patients with hemostatic defects related to liver disease usually bleed from a present lesion such as a gastric ulcer or esophageal varices due to alterations in any or all of the following: PT, PTT, platelets and/or fibrinogen.²¹

A decrease in platelets (thrombocytopenia) may be drug induced by stimulating an autoimmune response and will usually resolve within seven to ten days after the drug is discontinued. Harrison’s noted that once this response has been elicited, “only minute amounts of the drug are needed to set up subsequent reactions.”²² Platelet disorders include platelet dysfunction or a decrease in platelets and usually present with bleeding in the skin, mucous membranes and/or GI or genitourinary tract with petechiae as the hallmark presentation of thrombocytopenia. ACP Medicine²³ notes that purpura, gingival bleeding, menorrhagia, ecchymoses and recurrent

²⁰ Harrison’s Principles of Internal Medicine – 16th Ed. (2005), Part 5, Section 3 – Disorders of Hemostasis

²¹ Harrison’s Principles of Internal Medicine – 16th Ed. (2005), Part 5, Section 3 – Disorders of Hemostasis

²² Harrison Principles of Internal Medicine – Part 5, Section 3, 101. Disorders of the Platelets and Vessels, Drug-Induced Thrombocytopenia

²³ ACP Medicine (2007), XIII Platelet and Vascular Disorders

epistaxis, may also be seen with platelet disorders; however, Herkner et al.²⁴ reported epistaxis may be associated with hypertension, particularly sustained arterial hypertension.

Several commonly used drugs affect hemostasis. Patients on warfarin may experience bleeding ranging from ecchymoses to more serious bleeding, mostly GI and genitourinary; however, intracranial and internal bleeding may also be seen as warfarin effects coagulation factors and prolongs the PT.²⁵ The drug class of platelet aggregation inhibitors, which includes clopidogrel and ticlopidine, alter platelet aggregation resulting in a prolonged bleeding time but do not prolong the PT.²⁶ Purpura and epistaxis were commonly seen in clinical trials. Patients on ASA or NSAIDs may experience easy bruising and occasionally prolonged oozing after surgery particularly if the surgery involves the skin or mucous membranes due to inhibition of platelet release and aggregation as ASA and NSAIDs affect platelet aggregation and may prolong the PT. The most frequent adverse events for both the NSAIDs and ASA involve the GI tract which can include GI bleeding.^{27 28 29}

3.3 AERS CASE SERIES

The search strategy resulted in the identification and retrieval of 225 reports from the AERS database from which 55 reports were excluded. The excluded cases met the following exclusion criteria (in decreasing order of frequency):

Table 2: Reasons for Case Exclusion

Exclusion Reason	Number
Duplicate	18
Injury from fall	11
Bleeding disorder present prior to starting duloxetine	9
Liver failure	5
Onset of bleeding after duloxetine discontinued	3
Self-induced cutting	2
Motor Vehicle Accident	2
Aneurysm	1
Mallory-Weiss Tear	2
Bleeding from scratching	1
Miscoded	1
Total	55

²⁴ H. Herkner, A.N. Laggner and M. Mullner et al., Hypertension in patients presenting with epistaxis, Ann. Emerg. Med. 35 (2000), pp. 126–130.

²⁵ AHFS Drug Information (2007), 20:12.04.08 Coumarin Derivatives, Warfarin

²⁶ AHFS Drug Information (2007), 20:12.18 Platelet-aggregation Inhibitors, clopidogrel.

²⁷ Harrison's Principles of Internal Medicine – 16th Ed. (2005), Part 5, Section 3 – Disorders of Hemostasis

²⁸ AHFS Drug Information (2007), 28:08.04.92 Other Nonsteroidal Anti-inflammatory Agents, diclofenac

²⁹ AHFS Drug Information (2007), 28:08.04.24 Salicylates, aspirin

The final duloxetine case series included 170 unique cases. The outcomes of the 170 cases are placed into non-overlapping categories that include death, hospitalization, life-threatening, and required intervention such that each unique case is represented in a category. If a report is coded with more than one outcome, that report is placed in only one outcome category as determined by the outcome with the higher precedence. The outcome of death has a higher precedence than hospitalization, which is higher than life-threatening, which is higher than required intervention. For example, if a case is coded with hospitalization and life-threatening as outcomes, that case is assigned to the hospitalization category. Cases with non-serious outcomes or other serious outcomes that did not report death, hospitalization, life-threatening or required intervention are grouped together. When summed all outcomes equal the number of unique cases for the series.

The overall characteristics of the duloxetine case series are summarized in Table 3. Medical conditions and/or medications which might increase the risk for the reported bleeding event or platelet disorder were reported in 102 of the 170 cases. Thirty-nine of the patients reported concomitant use of anticoagulants, NSAIDs or ASA.

Table 3: Overall Characteristics of 170 Unique AERS Cases Reporting Bleeding Symptoms from Marketing to April 26, 2007

Location	US (131), Foreign (39)
Most Serious Outcome ³⁰	Death (6), Hospitalization (51), Life Threatening (2), Required Intervention (1), Other/Non-Serious (110)
Report Source	Expedited (100), Periodic (61), Direct (9)
Reporter	Health Care Provider (120), Consumer (50)
Gender	Male (49), Female (120), Unknown (1)
Age Range	Median (53 years), Range (17-88 years old), (n=148),
Peak Daily Dose	Median (60mg), Range (20-180mg), (n=152)
Onset Information	Median (14 days), Range (1-368 days), (n=73)
Offset Information	Median (5 days), Range (1-16 days), (n=9)
Indications for Use	Affective disorder (1), Anxiety (2), Bipolar disorder (1), Burn out syndrome (1), Chronic fatigue syndrome (1), Depression (78 ³¹), Fibromyalgia (5), Insomnia (1), Mood swing (1), Nervous system disorder (1), Neuropathy (14 ³²), OCD ³³ (1), Pain (8 ³⁴), Phantom limb pain (1), Post herpetic neuralgia (1), PTSD ³⁵ (1), Sciatica (1), Shingles (10), Stress (2), SUI ³⁶ (5), Uncalm nerves (1)
Duloxetine Disposition	Discontinued (104), continued (44), unknown (22)
Positive Dechallenge	Without treatment (43), With treatment (17)
Positive Rechallenge	(4)

³⁰ Unique cases with outcomes prioritized for serious as death, life threatening, hospitalization, required intervention, disability, congenital anomaly, other – Per Section B 2 of the Medwatch Form 3500

³¹ Depression (71), Depressive episode (1), MDD (5), Mild depression (1)

³² Diabetic neuropathy (2), DPNP (2), Facial neuropathy (1), Neuralgia (2), Neuropathic pain (1), Neuropathy (2), Neuropathy peripheral (4),

³³ OCD – obsessive-compulsive disorder

³⁴ Back pain (1), chronic pain (1), Pain (6)

³⁵ PTSD – post traumatic stress disorder

³⁶ SUI – Stress Urinary Incontinence

To facilitate analysis, the cases are further grouped by the System Organ Class as determined by MedDRA coding, and are ordered in descending frequency of reports. Cases with multiple sites of bleeding are grouped together.

Gastrointestinal (GI) System Bleeding (n=54)

The AERS case series included 54 unique cases of GI bleeding, with almost half occurring in the upper GI tract. Thirty-one cases reported either medical conditions and/or concomitant medications which may have increased the potential for the reported GI system bleeding event. A history of previous GI bleeding was described in one case. Fifteen cases were concomitantly using anti-coagulants, NSAIDs and/or ASA; with the majority (12/16) experiencing upper GI bleeding, two lower GI bleeding, and one case both upper and lower GI bleeding. Twenty-three were age 61 or older.

Table 4: Overall Characteristics of Unique AERS cases reporting GI System Bleeding from Marketing through April 26, 2007 (n=54)

Location:	US (41), Foreign (13)
Outcome	Death (2), Hospitalized (23), Other/Non-Serious (29)
Age	Median (58), range (17-88), (n=50)
Gender	Female (39), Male (14), Unknown (1), (n=54)
Peak Daily Dose	60mg, Range (20-180), (n=48)
Onset	Median (21 days), Range (1-120 days), (n=23)
Offset	Median (3 days), Range (1-6 days), (n=3)
Coded Preferred Terms ³⁷	GI Haemorrhage (12), Haemorrhage ³⁸ (2), Haemoptysis ³⁹ (1), Lower GI haemorrhage ⁴⁰ (19), Oral bleeding (3 ⁴¹) Upper GI haemorrhage ⁴² (25)
Concomitant Medication Drug Classes ⁴³ - labeled for reported gastrointestinal bleeding-related symptoms or increased bleeding ⁴⁴	Antihistamine (1), Antihyperlipidemic agent (1), Anti-infective agent (1), Cardiovascular agent (1), CNS ⁴⁵ agent (10), Endocrine and metabolic agent (3), Hematological agent (3), NSAID ⁴⁶ (7), Renal and genitourinary agent (4), Salicylic acid (8), SSRI (3)
Co-morbid Relevant Medical Conditions ⁴⁷	Chronic constipation (1), Colitis (1), Colon resection (1), Duodenal ulcer (1), ETOH abuse (1), Gastritis (1), H-pylori (1), IBS ⁴⁸ (2) Recurrent bleeding ulcers (1)
Identified Source of GI Bleeding	Bleeding ulcer (2), Diverticular bleeding (1), Duodenal bleeding (1), Duodenal

³⁷ A report may contain multiple terms, and therefore the sum of the events exceed the number of cases

³⁸ GI blood loss (1), blood on pillow in morning (1)

³⁹ Reported symptom - spitting up blood

⁴⁰ Lower GI haemorrhage (1), intestinal haemorrhage (1), large intestinal haemorrhage (1), diverticulum intestinal haemorrhagic (1), rectal haemorrhage (8), haematochezia (7)

⁴¹ Gingival bleeding (1), Mouth haemorrhage (1), Tongue haemorrhage (1)

⁴² Upper GI haemorrhage (1), gastric haemorrhage (2), gastric ulcer haemorrhage (2), duodenal ulcer haemorrhage (1), gastric ulcer perforation (1), small intestine haemorrhage (1), ulcer haemorrhage (1), haematemesia (10), Melena (5), Faeces discoloured (1),

⁴³ Drug Classes from Facts & Comparison 4.0

⁴⁴ One case may contain multiple medications labeled for reported gastrointestinal system symptoms or increased bleeding

⁴⁵ CNS – Central nervous system

⁴⁶ NSAID – non-steroidal anti-inflammatory drug

⁴⁷ One case may contain multiple co-morbid conditions

⁴⁸ IBS – irritable bowel syndrome

Table 4: Overall Characteristics of Unique AERS cases reporting GI System Bleeding from Marketing through April 26, 2007 (n=54)

	ulcer (1), Gastric bleeding (1), Gastric ulcer (2), ulcer (1), Jejunal ulcer (1), Pan-colitis (1), Rectal ulcer (1), Sore in mouth (1)
Duloxetine Disposition:	Discontinued (37), Continued (9), Unknown or Not Reported (8)
Positive Dechallenge	Without treatment (13), With treatment (8)

Death

Two cases reported death. The first case (ISR # 5159352) was a report from the literature of accidental death, where multiple drug intoxication was given as the cause of death. The second case is summarized below and reported the cause of death as secondary to GI hemorrhage.

ISR # 4800401, Foreign, Death

A physician reported the case of an 84 year old male who was prescribed duloxetine 60mg daily. Forty-three days after starting duloxetine, the patient “collapsed with melena” and was hospitalized. One day after the patient collapsed, the patient died from “cardiac arrest, secondary to hypovolemic shock, secondary to GI hemorrhage.” The patient was concomitantly taking multiple medications; however, the relevant medication for this assessment was diclofenac; although, the dose and duration of diclofenac was not provided. The patient’s medical history included dementia, COPD, HTN and agitation; and was negative for GI bleeding, anticoagulant use and alcohol use. The physician considered the event to be causally related to duloxetine.

Hospitalization

Twenty-three⁴⁹ cases reported hospitalization as the most serious outcome with 21 hospitalized for a GI system bleeding event. The two remaining cases, although experiencing GI bleeding were hospitalized for other reasons. Eighteen cases described either medical conditions and/or concomitant medications which may have increased the potential for the reported GI bleeding event, including three cases reporting use of warfarin and seven cases reporting use of NSAIDs and/or ASA⁵⁰. Two representative cases are summarized below:

ISR # 4791183, Foreign, Hospitalization+Life Threatening, Positive Dechallenge

A health care professional reported a case of a 61 year-old male who started duloxetine 60mg daily to treat depression. Six weeks after initiation of treatment, the patient was hospitalized for GI bleeding. Duloxetine was discontinued. The patient was reported recovering at the time of the report. The patient was concomitantly taking valproate, a drug product labeled for bleeding events.⁵¹ The case did not report any relevant medical history. The reporter considered the event to be causally related to duloxetine.

ISR # 4852897, US, Hospitalization, Positive Dechallenge

A psychiatrist reported a case of a 54 year-old female who started duloxetine 180mg daily to treat anxiety and depression. After two to three weeks of therapy, the patient experienced severe

⁴⁹ Three hospitalization cases were also coded with a life-threatening outcome

⁵⁰ ASA - acetylsalicylic acid (aspirin).

⁵¹ Valproic acid is labeled for thrombocytopenia, hemorrhage, bruising, and disorders of hemostasis/coagulation

stomach cramping and unexplained GI pain. Five days later, the patient was hospitalized for GI bleeding. Duloxetine was discontinued. The GI bleeding resolved. The patient's pain improved but had not resolved at the time of the report. No relevant medical history or concomitant medications were reported.

Elevated INR with concomitant use of Warfarin

The GI System included two cases of patients taking duloxetine and concomitantly using warfarin and experiencing GI bleeding. ISR # 4777942 is temporally associated with warfarin, rather than duloxetine and did not include any laboratory values. The second case is temporally associated with duloxetine and is summarized below.

ISR # 4549439, US, Clinical Trial, Hospitalization, Positive Dechallenge

A physician reported the case of a 76 year old female concomitantly receiving warfarin and participating in a clinical trial, who started duloxetine 80mg daily to treat stress urinary incontinence (SUI). On Day 21, the patient woke up with bright red emesis on her night gown, pillow and bed sheets. No coffee ground substance was noted. The patient did not experience any nausea prior to the event. She was hospitalized and duloxetine was discontinued. Her INR was 10.2, and PT 93.4. Treatment included two units of fresh frozen plasma and one unit of blood. No evidence of active GI bleeding was identified. She was discharged on Day 24 with an INR of 1.0. The patient had a history of GERD, hepatitis C, and a bowel resection with a colostomy. Her history was negative for bleeding and vomiting blood. The patient was on additional multiple medications, which had not changed prior to the event.

Vascular System⁵² (Organ and Tissue) Bleeding (n=38)

The AERS case series included 38 unique cases of vascular bleeding. The cases are included in the vascular system based on the coded MedDRA terms; however, the majority of the clinical presentations are internal bleeding or bleeding in the dermis. Twenty-four reported either medical conditions and/or concomitant medications which may have increased the potential for the reported vascular bleeding event. Four of the 38 cases were concomitantly using anti-coagulants, four ASA, and two NSAIDs. The most frequently reported symptom was ecchymosis and/or hematoma (24/38) with two cases presenting with petechiae and normal laboratory values. The characteristics of the vascular system group are summarized below.

Table 8: Overall Characteristics of Unique AERS cases reporting Vascular System Bleeding from Marketing through April 26, 2007 (n=38)

Location:	US (28), Foreign (10)
Outcome	Death (3), Hospitalized (14), Life threatening (2), Other/Non-serious (19)
Age	Median (57), Range (25-86), (n=33)
Gender	Female (23), Male (15)
Peak Daily Dose	Median (60 mg), Range (30-80), (n=36)
Onset	Median (22.5 days), Range (1-368 days), (n=20)
Offset	Median (7 days), Range (2-16 days), (n=3)

⁵² Organ and tissue bleeding, categorized as vascular bleeding by MedDRA PT terms

Table 8: Overall Characteristics of Unique AERS cases reporting Vascular System Bleeding from Marketing through April 26, 2007 (n=38)

Coded Preferred Terms ⁵³	Catheter site haemorrhage (1), Cerebral haemorrhage (5), Cerebral vascular accident (2), Contusion (4), Cutaneous vasculitis purpura (1), Ecchymosis (6), Haemorrhage (4), Haematoma (5), Hepatic haemorrhage (1), Increased tendency to bruise (4), Injection site bruising (4), Injection site haemorrhage (1), Operative haemorrhage (1), Petechiae (2), Purpura (1), Skin haemorrhage (1), Skin ulcer haemorrhage (1), Subarachnoid haemorrhage (1), Subdural haematoma (2), Traumatic haematoma (1), Vasculitis allergica hemorrhagic necrotic type (1)
Concomitant Medication Drug Classes ⁵⁴ - labeled for reported vascular system bleeding-related symptoms or increased bleeding ⁵⁵	Antihistamine (1), Antihyperlipidemic agent (2), Anti-infective agent (1), Biologic and immunological agent (1), Cardiovascular agent (2), CNS agent (5), Endocrine and metabolic agent (3), Hematological agent (4), NSAID (2), Renal and genitourinary agent (1), Salicylate (4), SSRI (1), Tricyclic (1)
Co-morbid Relevant Medical Conditions ⁵⁶	Aortic stenosis (1), Blood pressure increased (1), previous CVA (3), Endocarditis (1), Hypertension (1), ITP (1)
Duloxetine Disposition:	Discontinued (19), Continued (13), Unknown (6)
Positive Dechallenge	Without treatment (8), With treatment (2)

Death

Three cases in the vascular system group reported an outcome of death. One of the three cases (ISR # 4674574) described an 85 year-old female who experienced a cerebral hemorrhage and died one month after starting duloxetine. The case did not include concomitant medications or the patient's medical history. The second case (ISR # 4540780) reported vascular symptoms of petechial hemorrhage and ecchymosis on the extremities; however, the cause of death was listed as decompensated heart insufficiency with lung edema. The third case (ISR # 5260807) reported the cause of death as central pontine myelinosis due to rapid sodium level correction. The physician reported the patient experienced bleeding in an unspecified location "(not a stroke)" due to a low sodium level "which led to the seizure that caused the bleeding"

Hospitalization

Fifteen cases reported hospitalization, with seven of the hospitalizations reportedly due to the vascular system bleeding event. Intracranial bleeding was the most frequent location of vascular bleeding in the hospitalized patients. Eleven cases reported either medical conditions and/or concomitant medications which may have increased the potential for the reported vascular bleeding event, with one patient concomitantly using warfarin, and two ASA.

Positive Dechallenge

There were 11 cases in this group that reported positive dechallenge responses; eight of the dechallenge cases reported improvement and/or resolution with discontinuation of duloxetine only; and two cases reported improvement and/or resolution with discontinuation and medical treatment. Three representative positive dechallenge cases are described below.

⁵³ A report may contain multiple terms, and therefore the sum of the events exceed the number of cases

⁵⁴ Drug Classes from Facts & Comparison 4.0

⁵⁵ One case may contain multiple medications labeled for reported vascular system symptoms or increased bleeding

⁵⁶ One case may contain multiple co-morbid conditions

ISR # 4682981, US, Positive Dechallenge

A physician reported the case of a 35 year-old male who started duloxetine 30mg daily. The patient experienced “big black and blue” ecchymosis without any related injury. The patient discontinued duloxetine after two weeks of therapy. The bruising resolved. The patient was not taking any concomitant medications.

ISR # 5036917, Foreign, Positive Dechallenge

A physician reported a case of a female who started on duloxetine 60mg daily for treatment of peripheral neuropathy. On Day 12, the patient experienced diffuse skin hemorrhage with large confluent purpuric lesions in the abdomen, legs and arms. All of the coagulation parameters were found to be normal. Duloxetine was discontinued on Day 12. The patient recovered. The reporting physician considered the event related to duloxetine.

ISR # 5120484, Foreign, Positive Dechallenge

A physician reported the case of a 42 year old male who started duloxetine 60mg daily for treatment of depression. On Day 4, the patient experienced pain in his arms and knees. The patient developed hematomas in many areas including upper arms, shoulders, elbows and knees. Duloxetine was discontinued. The hematomas abated two days after discontinuation of duloxetine therapy. The patient was not taking any other medications but had experienced similar symptoms with benzoic acid chorothymol and salicylic acid thymol. The physician saw a causal relationship between the event and duloxetine.

Multi-system Bleeding (n=27)

The AERS case series included 27 unique cases with reports of multi-system bleeding. Fifteen of the 27 cases reported either medical conditions and/or concomitant medications which may have increased the potential for the reported bleeding event; with six cases concomitantly using anti-coagulants, and three ASA. Four patients presented with petechiae; one with normal laboratory values, two diagnosed with thrombocytopenia and one without laboratory results. The characteristics of the multi-system bleeding group are summarized below.

Table 8: Overall Characteristics of Unique AERS cases reporting Multi-system bleeding from Marketing through April 26, 2007 (n=27)

Outcome	Hospitalization (8), Life threatening (1), Required intervention (1), Other/Non-serious (17)
Age	Median (48), Range (33-83), (n=22)
Gender	Female (18), Male (9)
Peak Daily Dose	Median (60), Range (30-120), (n=23)
Onset	Median (16 days), Range (5-111 days), (n=9)
Offset	5 days, (n=1)
Coded Preferred Terms ⁵⁷	Activated PTT time prolonged (1), CVA (1), Coagulopathy (3), Contusion (3), Diarrhea hemorrhagic (1), Epistaxis (4), Faeces discoloured (2), GI haemorrhage (2), Gingival bleeding (2), Haematochezia (2), Haematemesis (1), Haematoma (3), Haematotympanum (1), Haemorrhage (2), Haemorrhage

⁵⁷ A report may contain multiple terms, and therefore the sum of the events exceed the number of cases

Table 8: Overall Characteristics of Unique AERS cases reporting Multi-system bleeding from Marketing through April 26, 2007 (n=27)

	urinary tract (2), Injection site bruising (1), INR ratio increased (3), Intracranial haemorrhage (1), Metrorrhagia (1), Mouth haemorrhage (2), Mucosal haemorrhage (2), Occult blood positive (1), Petechiae (4), Platelet count decreased (4), Platelet disorder (1), Post procedural haemorrhage (1), PT prolonged (3), Purpura (1), Rectal haemorrhage (3), RBC urine positive (1), Scleral haemorrhage (1), Skin discolouration (1), Skin haemorrhage (1), Subdural haemorrhage (1), Thrombocytopenia (5), Vaginal haemorrhage (4), Vessel puncture site bruise (1),
Concomitant Medication Drug Classes ⁵⁸ - labeled for reported bleeding related symptoms or increased bleeding ⁵⁹	Anithyperlipidemic agent (1), CNS agent (6), Dietary supplement ⁶⁰ (1), Endocrine and metabolic agent (1), Hematological agent (6), Renal and genitourinary agent (2), Salicylate (3)
Co-morbid Relevant Medical Conditions ⁶¹	Congenital thrombocyte dysfunction (1), Hepatitis C (1), Infectious colitis (1), ITP (1), Possible cervical cancer (1), Possible leukemia (1)
Duloxetine Disposition:	Discontinued (18), Continued (6), Unknown (1)
Positive Dechallenge	Without treatment (7), With treatment (3)
Positive Rechallenge	2

Hospitalization

Eight cases reported hospitalization as the most serious outcome, including two positive rechallenges. Six cases reported either medical conditions and/or concomitant medications which may have increased the potential for the reported bleeding event, including two cases concomitantly using anti-coagulants, and one ASA. A positive rechallenge case is summarized below.

ISR # 4877819, US, Positive Dechallenge/Positive Rechallenge

A nurse practitioner reported the case of a 36 year old male who started duloxetine 30mg daily to treat depression. Three to five days later, the patient experienced bleeding from his nose, mouth, and anus and vomited blood. Duloxetine was discontinued. The bleeding stopped. A week later, duloxetine was restarted. The bleeding resumed. Duloxetine was discontinued. The patient was not taking any concomitant medications. The nurse practitioner considered the event related to duloxetine.

Platelet Disorders

Platelet disorders were the most frequently reported event (10/27) in the multi-system bleeding group, with five cases coded for thrombocytopenia, one a platelet disorder, and four a decreased platelet count. Six of the patients were hospitalized including four reporting thrombocytopenia, one a platelet disorder and one a decreased platelet count.

⁵⁸ Drug Classes from Facts & Comparison 4.0

⁵⁹ One case may contain multiple medications labeled for reported symptoms or increased bleeding

⁶⁰ COQ10

⁶¹ One case may contain multiple co-morbid conditions

Four cases reported a decreased platelet count but did not include a diagnosis of thrombocytopenia and are described briefly. The first case reported a decreased platelet count in a 51 year-old patient concomitantly using warfarin and noted that *“the patient’s platelet count was normally 40,000 and that it was only 34 upon admission to the hospital.”* A platelet count of 10,000 was reported in the second case for a male of unknown age who experienced bleeding from his *“gums and nose”* during duloxetine therapy. The third case documented a platelet count of 145000cells/mm³ in a patient with hemorrhagic diarrhea. The fourth case involved a 33 year-old female consumer who reported an increased frequency of menses with intermittent spotting and a low platelet count but did not include any specific laboratory results.

Five cases of thrombocytopenia were reported with two summarized in detail below. A brief description of the three remaining cases follows. The first case described a 40 year-old female experienced thrombocytopenia (66,000) and elevated liver functions resulting in hospitalization after 35 days of duloxetine therapy. The second case involved a 64 year-old male patient with a history of idiopathic thrombocytopenia (ITP) was hospitalized after experiencing spontaneous subdural bleeding after two weeks of duloxetine therapy and was found to have a thrombocyte count of 30 X10⁹/L. In the third case, an 83 year-old female was hospitalized for dehydration, orthostatic hypotension, electrolyte imbalance and a urinary tract infection; however, her discharge diagnosis was a non-ST myocardial infarction, thrombocytopenia, infectious gastroenteritis and colitis and peptic ulcer. No laboratory results were provided. In addition to the two remaining thrombocytopenia cases, the single case reporting a platelet dysfunction is summarized below.

ISR # 4853476, Foreign, Hospitalization, Positive Dechallenge/Positive Rechallenge

A physician reported a case of a 33 year-old female who started duloxetine 60mg daily to treat a severe episode of depression. After 110 days of therapy, she experienced hematomas all over her body with generalized weakness, pruritis and later hematorrhea. “Basal blood clotting factors” were normal. Fibrinogen was in the middle range – 339 mg/dl. Bleeding time was at the upper limit of the normal range – 9.0 minutes. Aggregation was slightly constricted. Aggregation of thrombocytes with adenosine showed no reaction resulting in a diagnosis of medium thrombocyte dysfunction. Duloxetine was discontinued. The patient’s hematomas were recovering when duloxetine was restarted. She developed new hematomas. Discontinuation of duloxetine was recommended. The physician saw a causal relationship between the event and duloxetine.

ISR # 4852906, US, Life Threatening + Hospitalization, Positive Dechallenge

A physician reported the case of a female patient who started duloxetine 60mg daily for treatment of post-herpetic neuralgia. After two weeks, the patient was hospitalized with severe thrombocytopenia and a platelet count of 6,000. A head CT revealed a left parietal cortical hemorrhage. The patient was treated with prednisone and discharged with an improved platelet count that had not returned to the normal range. Duloxetine was discontinued. The patient was not taking any medications and had a normal platelet count nine months prior to the duloxetine therapy. The physician considered the event possibly related to duloxetine.

ISR # 5300912, Foreign, Positive Dechallenge

A psychiatrist reported the case of a 46 year-old male who started duloxetine 60mg daily for treatment of depression. On Day 16, the patient experienced petechiae on his toes, night sweats and urination problems. On Day 30, a thrombocyte count of 49,350 was reported. Duloxetine was discontinued. The petechiae resolved. Eighteen days after stopping duloxetine, the platelet count had increased to 79,275. Three weeks later, a further increase was seen with a platelet count of 87,675. The psychiatrist considered the events possibly related to duloxetine.

Elevated INR

The multi-system bleeding group included four cases of elevated INR and one case with a decreased quick value after beginning duloxetine. Two representative cases are summarized below.

ISR # 5152905, US, Required Intervention

A pharmacist reported the case of a 74 year-old male who started duloxetine daily for treatment of sciatica. The patient experienced a slow rise in INR values over one month. Bleeding between his toes and at venipuncture and injection sites prompted the patient to seek treatment in the ER. The patient was treated with Vitamin K and the warfarin was held. The patient restarted the warfarin and his INR level rose again. Duloxetine was discontinued and the INR stabilized. The patient was on warfarin and Lovenox® concomitantly but his medications, diet and health issues were stable prior to the administration of duloxetine. The patient had normal liver functions and did not drink alcohol.

ISR # 4538855, US, Hospitalization

A nurse reported the case of a 53 year-old female who started duloxetine 60mg QD for depression. The patient was on concomitant warfarin therapy after a heart valve replacement. On Day 14, her INR was 1.81 and her PT was 18.3. On Day 49, the patient experienced severe bruising and rectal bleeding and was hospitalized. Her PT was 141.1. Duloxetine was discontinued. The patient was treated with packed red blood cells and Vitamin K injections. She had not changed her dietary habits and had not taken any new medications, including over-the-counter medications and also had not experienced nausea, vomiting or anorexia after initiating duloxetine therapy. The patient's PT levels had remained stable for at least a couple of months before starting duloxetine. Twenty-two days after discontinuing duloxetine, the patient's PT was 33.2; her INR was 3.43 with resolution of the bleeding and bruising. The nurse considered the event related to duloxetine as other causes had been ruled out.

Renal and Urinary System Bleeding (n=17)

The AERS case series included 17 unique cases with reports of bleeding in the renal and urinary system. Eleven of the 17 cases reported either medical conditions and/or concomitant medications which may have increased the potential for reported renal and urinary system bleeding event. Three were concomitantly using ASA, and one an anti-coagulant. No abnormal PT or platelet values were reported for the renal and urinary system cases.

Table 8: Overall Characteristics of Unique AERS cases reporting Renal and Urinary System bleeding from Marketing through April 26, 2007 (n=17)

Outcome	Death (1), Hospitalization (2), Other/Non-serious (14)
Age	Median (52), Range (31-83), (n=14)

Table 8: Overall Characteristics of Unique AERS cases reporting Renal and Urinary System bleeding from Marketing through April 26, 2007 (n=17)

Gender	Female (12), Male (5), (n=17)
Peak Daily Dose	Median (60), range (30-80), (n=15)
Onset	Median (4 days), Range (1-45 days), (n=5)
Offset	Median (2), Range (1-2), (n=2)
Coded Preferred Terms ⁶²	Blood urine present (8), Haemorrhaging urinary tract (1), Hematuria (7), Renal haemorrhage (1), (n=17)
Concomitant Medication Drug Classes ⁶³ - labeled for reported renal or urinary system related bleeding symptoms or increased bleeding ⁶⁴	Anti-infective agent (1), Cardiovascular agent (1), CNS agent (4), Hematological agent (1), Renal and genitourinary agent (1), Salicylate (3), SSRI (1)
Co-morbid Relevant Medical Conditions ⁶⁵	Chronic renal insufficiency (1), Chronic UTI (1), UTI (2)
Duloxetine Disposition:	Discontinued (9), Continued (5), Unknown (3)
Positive Dechallenge	Without treatment (4), with treatment (1)
Positive Rechallenge	1

Death

One case was coded with death. The patient was hospitalized due to Stevens Johnson Syndrome and pulmonary emboli with the cause of death reported as congestive heart failure. During the hospitalization, the patient developed bleeding in the kidneys which was reported as related to heparin and resolved with adjusting the heparin dose.

Hospitalization

Two cases were coded with hospitalization as the most serious outcome with both concomitantly using ASA. The first case described a patient who was admitted with confusion, insomnia, anorexia and shortness of breath with the admitting urinalysis positive for blood. The second case (hospitalized for psychiatric reasons), also a positive dechallenge case, is summarized below.

ISR # 4821857, Foreign, Hospitalization, Positive Dechallenge

A physician reported the case of a male who started duloxetine 60mg daily for treatment of depression. During a psychiatric hospitalization, he experienced a “massive haematuria and a prolongation of hospitalization.” Duloxetine was discontinued. The patient fully recovered from the haematuria. No relevant medical history was reported; however the patient was concomitantly using aspirin, although the dose and duration of use were not provided. The reporting physician saw a causal relationship between the event and duloxetine.

⁶² A report may contain multiple terms, and therefore the sum of the events exceed the number of cases

⁶³ Drug Classes from Facts & Comparison 4.0

⁶⁴ One case may contain multiple medications labeled for reported renal and urinary symptoms or increased bleeding

⁶⁵ One case may contain multiple co-morbid conditions

Positive Dechallenge/Positive Rechallenge

The renal and urinary system group included one positive dechallenge/positive rechallenge case, and five positive dechallenge cases. The dechallenge/rechallenge case is summarized below:

ISR # 5201156, US, Positive Dechallenge/Positive Rechallenge

A psychiatric nurse practitioner reported the case of a 47 year-old female who started duloxetine 60mg daily. The patient experienced frank urinary bleeding. Duloxetine was discontinued. The bleeding resolved. After re-starting duloxetine, the patient again experienced frank urinary bleeding. Duloxetine was discontinued and the bleeding again stopped. The patient did not have any relevant history and was taking clonazepam concomitantly. The nurse practitioner assessed the event as related to the duloxetine. Verbal follow-up with the reporter indicated that the patient was re-challenged a third time (starting at lower doses) without a recurrence of bleeding. The patient's primary care physician was unable to identify any alternative etiology for the frank urinary bleeding.

Reproductive System Bleeding (n=16)

The AERS case series included 16 unique cases with reports of increased or abnormal bleeding in the reproductive system bleeding. Seven of the sixteen cases have either medical conditions and/or concomitant medications which may have increased the potential for reproductive system bleeding event. No concomitant use of anti-coagulants, ASA or NSAIDs was reported.

Table 5: Overall Characteristics of Unique AERS cases reporting Reproductive System Bleeding from Marketing through April 26, 2007 (n=16)

Outcome	Hospitalization (1), life threatening (1), Other/Non-serious (14)
Age	Median (36.5), Range (17-58) (n=14)
Gender	Female (16)
Peak Daily Dose	50mg, Range (30-120), (n=16)
Onset	Median (9 days), range (1-32 days), (n=8)
Coded Preferred Terms ⁶⁶	Metrorrhagia (11), Polymenorrhea (1), Postmenopausal hemorrhage (1), Vaginal hemorrhage (4)
Concomitant Medication Drug Classes ⁶⁷ - labeled for reported reproductive system related bleeding symptoms or increased bleeding ⁶⁸	CNS agent (5), SSRI (1)
Co-morbid Relevant Medical Conditions ⁶⁹	ETOH abuse (1), Hyperplastic uterus (1)
Duloxetine Disposition:	DC (7), Continued (8), Unknown (1)
Positive Dechallenge	Without treatment (5), With treatment (1)
Positive Rechallenge	1

⁶⁶ A report may contain multiple terms, and therefore the sum of the events exceed the number of cases

⁶⁷ Drug Classes from Facts & Comparison 4.0

⁶⁸ One case may contain multiple medications labeled for increased bleeding or reported reproductive system symptoms

⁶⁹ One case may contain multiple co-morbid conditions

Serious Outcomes

Two cases in this group reported serious outcomes unrelated to the bleeding event; one hospitalization and one life-threatening. The hospitalized patient was not taking any concomitant medications. The first case (hospitalization was related to thoracic pain) described post-menopausal bleeding after six months without menstruation. The second case (life-threatening outcome related to suicidal ideations) described vaginal bleeding that lasted for one month.

Positive Dechallenge

The reproductive system group included seven dechallenge cases, with six dechallenge cases reporting improvement and/or resolution with discontinuation of duloxetine only; and one case reporting improvement and/or resolution with discontinuation and medical treatment. A representative positive rechallenge case is summarized below:

ISR # 5150579, Foreign, Positive Dechallenge/Positive Rechallenge

A pharmacist reported the case of a 43 year-old female who started duloxetine 60mg daily for the treatment of depression. The patient had not experienced menstruation for two years. On Day 2, the patient experienced vaginal bleeding. The bleeding occurred on approximately 50% of the days the patient was taking duloxetine. The vaginal bleeding was confirmed by a gynecologist. Duloxetine was discontinued and the vaginal bleeding stopped. The patient restarted duloxetine and again experienced vaginal bleeding. At the time of the report, the patient was continuing duloxetine as the medication was effectively treating her depression. The patient's concomitant medications were prazepam for insomnia and levonorgestrel for contraception. The patient also took mirtazapine for 10 days concomitantly with duloxetine but did not experience vaginal bleeding while on mirtazapine. The pharmacist considered the event related to duloxetine.

Respiratory System Bleeding (n=10)

The AERS case series included 10 unique cases with reports of bleeding in the respiratory system. Six cases detailed either medical conditions and/or concomitant medications which may have increased the potential for the reported respiratory system bleeding event with one patient concomitantly using an NSAID. No concomitant use of anticoagulants or ASA was noted. In addition, no abnormal platelet counts or PT values were reported. Four cases reported increased blood pressure after beginning duloxetine therapy with two reporting a history of hypertension.

Table 6: Overall Characteristics of Unique AERS cases reporting Respiratory System Bleeding from Marketing through April 26, 2007 (n=10)

Location	US (7), Foreign (3)
Outcome	Hospitalized (1), Other/Non-serious (9)
Age	Median (60.5), Range (33-85), (n=7)
Gender	Female (6), Male (4)
Peak Daily Dose	60mg, Range (30-120), (n=8)
Onset	Median (1.5 days), Range (1-5 days), (n=4)

Table 6: Overall Characteristics of Unique AERS cases reporting Respiratory System Bleeding from Marketing through April 26, 2007 (n=10)

Offset	5 days, (n=1)
Coded Preferred Terms ⁷⁰	Epistaxis (9), Haemoptysis (1), (n=10)
Concomitant Medication Drug Classes ⁷¹ -labeled for reported respiratory symptoms related bleeding or increased bleeding ⁷²	CNS agent (1), Respiratory agent (2), NSAID (1)
Co-morbid Relevant Medical Conditions ⁷³	Arterial hypertension (1), asthma (1), hypertension (3), hypertensive crisis (1)
Duloxetine Disposition:	Discontinued(8), Continued (1), Unknown (1)
Positive Dechallenge	Without treatment (3), With treatment (1)

Hospitalization

The hospitalization was due to a hypertensive crisis with epistaxis in a patient with a reported history of well-controlled arterial hypertension with no concomitant use of anticoagulants, ASA or NSAIDs.

Positive Dechallenge

Four positive dechallenges were described; three dechallenge cases reporting improvement and/or resolution with discontinuation of duloxetine only; and one case reporting improvement and/or resolution with discontinuation and medical treatment. A representative positive dechallenge is summarized below.

ISR # 4683133, US, Positive Dechallenge

A 66 year-old female consumer reported starting duloxetine 30mg daily. She experienced bleeding from her nose as well as nausea, chest pain, constipation, exhaustion and increased pain in her legs. Duloxetine was discontinued and the nose bleeds stopped. The patient was also taking atenolol and simvastatin.

Otic and Ophthalmic Bleeding (n=8)

The AERS case series included 8 unique cases with reports of bleeding in the eye and/or ear but did not include any cases with serious outcomes. Although none of the cases reported use of anti-coagulants, ASA or NSAIDs, seven described either medical conditions and/or concomitant medications which may have increased the potential for the reported eye and/or ear bleeding event. Specific onset and offset were not reported for any of the cases in this group. One case reported both concomitant medications and co-existing medical condition which may have increased the risk of the reported eye hemorrhage; however, the case described a positive dechallenge response when the duloxetine was discontinued.

⁷⁰ A report may contain multiple terms, and therefore the sum of the events exceed the number of cases

⁷¹ Drug Classes from Facts & Comparison 4.0

⁷² One case may contain multiple medications labeled for reported respiratory system symptoms or increased bleeding

⁷³ One case may contain multiple co-morbid conditions

Table 7: Overall Characteristics of Unique AERS Cases Reporting Otic and Ophthalmic Bleeding from Marketing through April 26, 2007 (n=8)

Location	US (8)
Outcomes	Other/Non-serious (8)
Age	Median (47.5), Range (26-65), (n=8)
Gender	Female (6), Male (2), (n=8)
Peak Daily Dose	Median (60), Range (30-60), (n=7)
Coded Preferred Terms ⁷⁴	Ear haemorrhage (1), Eye Haemorrhage (6), Retinal haemorrhage (1)
Concomitant Medication Drug Classes ⁷⁵ - labeled increased bleeding ⁷⁶	CNS agent (1), Endocrine and metabolic agent (2)
Co-morbid Relevant Medical Conditions ⁷⁷	IDDM ⁷⁸ (2), Hypertension (2)
Duloxetine Disposition:	Discontinued (4), Continued (2), Unknown (2)
Positive Dechallenge	2

Summary Chart

A chart of the basic characteristics of the body system groups is summarized below.

Table 8. Summary of Characteristics of All Body System Groups

	Serious Outcomes death, hospitalization, life threatening	Median age	Median onset	Median offset	Positive Dechallenge	Positive Rechallenge	NSAID, ASA or anti-coagulants
GI (54)	25	58	21	3	21	0	15
Vascular (38)	19	60	22.5	7	10	0	11
Multi-System (27)	9	48	16	5	10	2	9
Renal (17)	3	52	4	2	5	1	4
Reproductive (16)	2	36.5	9	NA	6	1	0
Respiratory (10)	1	60.5	1.5	5	4	0	1
Otic & Ophthalmic (8)	0	47.5	NA	NA	2	0	0

Drug Use

The Duloxetine NME Postmarketing Review performed on March 13, 2007 included drug use information stratified by age and gender which are summarized in Tables 9 and 10 below:

⁷⁴ A report may contain multiple terms, and therefore the sum of the events exceed the number of cases

⁷⁵ Drug Classes from Facts & Comparison 4.0

⁷⁶ One case may contain multiple medications labeled for reported ear and eye symptoms or increased bleeding

⁷⁷ One case may contain multiple co-morbid conditions

⁷⁸ IDDM – insulin dependent diabetes mellitus

Table 9. Duloxetine Adverse Event Reports in AERS Database by Age Category⁷⁹

Age Group	Adverse Event Reports (%) from August 2004 to February 2007	Drug Use – TRx (%) from August 2004 to December 2006
0 – 5 years	16/5671 (0.3%)	1,354 (0.0%)
6 yrs – 16 yrs	39/5671 (0.7%)	24,696 (0.6%)
17 yrs – 30 yrs	399/5671 (7.0%)	314,749 (7.8%)
31 yrs – 40 yrs	697/5671 (12.3%)	519,301 (15.2%)
41 yrs – 50 yrs	937/5671 (16.5%)	823,357 (27.4%)
51 yrs – 60 yrs	929/5671 (16.4%)	756,469 (26.3%)
61 yrs – 70 yrs	549/5671 (9.7%)	367,467 (11.9%)
71 yrs +	583/5671 (10.3%)	329,656 (10.0%)
Unknown	1522/5671 (26.8%)	63,085 (0.8%)

Table 10. Duloxetine Adverse Event Reports in AERS Database by Gender

	Adverse Event % August 2004 to February 28, 2007	Drug Use – Total Prescriptions % from August 2004 through December 2006
Female	73% (4140/5671)	73% (10,198,586/14,016,887)
Male	26% (1474/5671)	26% (3,684,624/14,016,887)
Unknown	1% (57/5671)	1%

4 DISCUSSION

The duloxetine post-marketing case series included 170 unique cases with reports of bleeding. While GI system bleeding was the most frequently reported location of bleeding, bleeding was also reported in locations throughout the body and ranged in severity from bruising to a fatal GI hemorrhage. Medical conditions and/or concomitant medications which may increase the risk of bleeding were reported in 102 of the cases. Six reports of death were included in the case series. Four⁸⁰ of the deaths were unrelated to duloxetine; however, a role for duloxetine cannot be excluded in two of the deaths.⁸¹ In addition, 33 of 51 hospitalizations were reportedly due to the bleeding event, with one death and 12 hospitalizations concomitantly using anti-coagulants, ASA and/or NSAIDs. The case series included 60 positive dechallenges, but most compelling were the four positive rechallenges.

⁷⁹ Verispan, LLC: Total Patient Tracker, Aug04-Dec06, Extracted Feb07. Files: TPT Cymbalta AUG04-DEC06 Aggregate Product Brand Report.xls, TPT Cymbalta aug04-dec06 Aggregate Gender Report.xls

⁸⁰ ISR # 4540780 – decompensated heart insufficiency with lung edema, ISR # 5260807 – central pontine myelinosis due to rapid sodium level correction, ISR # 5159352 – accidental death due to multiple drug intoxication, ISR # 4860668 – congestive heart failure

⁸¹ ISR #4674574 – cerebral hemorrhage, ISR # 4800401 – cardiac arrest secondary to hypovolemic shock secondary to GI hemorrhage

Gastrointestinal bleeding was the most frequently reported event with 28% (15/54) concomitantly using NSAIDs, ASA and/or anticoagulants. Studies show that concomitant use of NSAIDs, anti-coagulants and/or ASA, and SSRIs resulted in an increased risk of upper GI bleeding that in some cases was more than the additive effect of the drugs. The SSRI labels address the concomitant use of NSAIDs, ASA and/or anticoagulants in the Drug Interactions and Patient Information sections. The duloxetine label does not mention the concomitant use of drugs which can affect hemostasis but does reference rare cases of hematochezia and melena under the clinical trials section.

Thirty-five post-marketing cases reported dermal or mucosal bleeding. The current labeling notes infrequent increased tendency to bruise and rare ecchymosis was seen in the clinical trials.

Thirteen cases of epistaxis were described with four cases also reporting a concurrent increase in blood pressure. Two of the four had a history of hypertension; one with arterial hypertension who described a hypertensive crisis after initiation of duloxetine. Duloxetine is currently labeled for hypertensive crisis in the postmarketing reports and increased blood pressure in Precautions but does not mention epistaxis.

Nine cases of decreased platelets and one case with platelet dysfunction were included in the case series. Additional cases of decreased platelets may be included in the post-marketing cases; however, the majority of the cases did not include laboratory values, or a diagnosis of thrombocytopenia. While a small portion of the cases (n=3) reported normal coagulation results with the presence of clinical symptoms such as petechiae, Halperin and Reber noted that hemostasis tests have a low sensitivity and approximately 50% of the bleeding cases they reviewed had normal coagulation tests. The current labeling includes a reference to rare cases of thrombocytopenia in clinical trials.

A possible drug interaction with warfarin was noted in five cases reporting increases in the PT/INR after initiating duloxetine, in addition to one case reporting a decreased quick time with use of phenprocoumon. These cases point to an additional factor of hemostasis that may be affected by duloxetine. The current duloxetine label includes a section in Drug-Drug Interactions addressing the possibility of adverse events with highly protein bound drugs but does not specifically mention warfarin.

Coagulation is a complex process with serotonin playing an important though unexplained role. As the literature noted, serotonin may affect a number of factors during the hemostatic process. The OSE case series and the literature support that conclusion as a temporal association with altered platelet function, decreased platelets and increased PT levels was seen in the duloxetine post-marketing cases.

OSE previously evaluated a potential association between drugs that inhibit serotonin and an increased risk of bleeding. In May of 2000, OSE analyzed SSRI post-marketing reports and concluded that SSRI use “may contribute to an increased risk of bleeding in various body systems” which “may be associated with serious outcomes including death or disability.”⁸² DPP

⁸² OPDRA Postmarketing Safety Review, Hemorrhages with Serious Outcomes, Kathleen Phelan, May 8, 2000

considered the evidence in the literature and the post-marketing reports sufficient⁸³ support of an increased risk for bleeding with serotonin inhibitors and requested SSRI class labeling for abnormal bleeding. The duloxetine post-marketing cases duloxetine and the literature for both duloxetine and venlafaxine continue to support a potential increased risk of bleeding with use of drugs that inhibit serotonin.

5 CONCLUSION

The duloxetine case series and the current literature is supportive an increased risk of bleeding with drugs that inhibit serotonin, particularly in those patients using ASA, anticoagulants and/or NSAIDs. The literature has urged health care providers to use caution when prescribing a drug that inhibits serotonin to patients of advanced age, patients with a medical condition which might affect hemostasis and patients concomitantly using drugs which affect hemostasis. An increased risk may also be present for patients with an underlying hemostatic defect, either a coagulation defect or a platelet dysfunction. As of December 2006, over 3 million patients were prescribed duloxetine. Adding language similar to the SSRIs (see 1.3 Product Labeling) to the Precautions, Drug Interactions and Patient Information sections in both SNRI labels, duloxetine and venlafaxine, will alert the practicing community and patients to potential bleeding complications with SNRI therapy.

RECOMMENDATIONS

- 1 Consider adding the precaution for “abnormal bleeding” found in the SSRI labels to the SNRI (duloxetine and venlafaxine) labels. Also consider adding language describing duloxetine associated thrombocytopenia or platelet dysfunction.
- 2 Consider adding the drug interaction language for warfarin and drugs that affect hemostasis (ASA, NSAIDS and anticoagulants) found in the SSRI labels to the SNRI labels.
- 3 Consider adding patient information language regarding concomitant use of ASA, NSAIDs or anticoagulants found in the SSRI labels to the SNRI labels.

⁸³ Hughes, Alice and Judith Racoosin, Review and Evaluation of Clinical Data, November 19, 2003

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APPENDICES

APPENDIX 1: DATA MINING DESCRIPTION

A data mining analysis of the Adverse Event Reporting System (AERS) database was performed for this review using WebVDME 6.0. The analysis uses the Multi-item Gamma Poisson Shrinker (MGPS)^{84 85} algorithm which analyzes the records contained in the AERS database. The algorithm then quantifies reported drug-event associations by producing a set of values or scores which indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting rate of an event for a particular drug relative to all other drugs and events in the database. MGPS also calculates lower and upper 90% confidence limits for the EBGM values, denoted EB05 and EB95 respectively.

EBGM values indicate the strength of the reporting relationship between a particular drug and event, as reported in AERS. For example, if EBGM=10 for a drug-event combination, then the drug-event occurred 10 times more frequently in the database than statistically expected when considering all other drugs and events in AERS database as a background, or expected. A drug-event combination having an EB05 ≥ 2 indicates 95% confidence that this drug-event combination occurs at least twice the expected rate when considering all other drugs and events in the database. A drug-event combination having an EB05 > 1 indicates 95% confidence that this drug-event combination occurs at least at a higher-than-expected rate considering all other drugs and events in the database.

The higher the EBGM score and accompanying EB05, EB95 confidence intervals for a particular drug-event, the higher the association is between that drug and event, given the database being analyzed. Note that this association is a result of the relative reporting for various events among all drugs in the database. The degree of this association in all patients exposed to the drug worldwide, however, cannot be elicited from an MGPS data mining analysis alone, because the association scores from such an analysis are generated from the specific database analyzed—in this case, AERS, which consists of spontaneous adverse events reports. Also, an elevated EBGM score of association for a particular drug-event combination does not prove causality or an increased relative risk of that drug-event. Similarly, the absence of an elevated EBGM score for a drug-event cannot be interpreted as a definite lack of toxicity for that drug-event. Finally, reporting and detection biases can occur and effects of concomitant illnesses or therapy cannot be fully controlled in data mining analyses using MGPS. Because of the spontaneous nature of reporting, the results should not be interpreted as a formal comparison of treatment groups or of their relative risks.

APPENDIX 2: LIMITATION OF AERS

The voluntary or spontaneous reporting of adverse events from health care professionals and consumers in the U.S reflects underreporting and also duplicate reporting. For any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s). The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues. Therefore, counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing drug risk between drugs.

APPENDIX 3: VERISPAN DRUG USE

VERISPAN, LLC

Vector One®: National (VONA)

Verispan's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2 billion prescription claims, representing over 160 million unique patients.

The number of dispensed prescriptions is obtained from a sample of virtually all retail pharmacies throughout the U.S and represents approximately half of the retail prescriptions dispensed nationwide. Verispan receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

⁸⁴ DuMouchel W, Pregibon D. Empirical bayes screening for multi-item associations. Proceedings of the conference on knowledge discovery and data; 2001 Aug 26-9; San Diego (CA): ACM Press: 67-76.

⁸⁵ Szarfman A, Machado SG, O'Neill RT. Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the U.S. FDA's spontaneous reports database. Drug Safety 2002; 25: 381-92.

VERISPAN, LLC**Vector One[®]: Total Patient Tracker (TPT)**

Verispan's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes.

TPT derives its data from the Vector One[®] database which integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, pharmacy benefits managers and their data systems, physician offices and hospitals. Vector one receives over 1.8 billion prescription claims per year, which represents over 150 million patients tracked across time.

APPENDIX 4: MedDRA SMQ Preferred Terms for SMQ Haemorrhage (excluding laboratory terms)**SMQ Haemorrhage terms (excl laboratory terms)**

Basal ganglia haemorrhage	Duodenitis haemorrhagic	Haemorrhagic transformation stroke	Operative haemorrhage	Skin haemorrhage
Abdominal haematoma	Dysfunctional uterine bleeding	Haemorrhagic tumour necrosis	Optic disc haemorrhage	Skin ulcer haemorrhage
Acute haemorrhagic leukoencephalitis	Ear haemorrhage	Haemorrhagic urticaria	Optic nerve sheath haemorrhage	Small intestinal haemorrhage
Adrenal haematoma	Ecchymosis	Haemorrhoidal haemorrhage	Oral mucosal petechiae	Small intestinal ulcer haemorrhage
Adrenal haemorrhage	Encephalitis haemorrhagic	Haemothorax	Osteorrhagia	Soft tissue haemorrhage
Anal haemorrhage	Enterocolitis haemorrhagic	Henoch-Schonlein purpura	Ovarian haematoma	Spermatic cord haemorrhage
Anal ulcer haemorrhage	Epistaxis	Hepatic haemangioma rupture	Ovarian haemorrhage	Spinal cord haemorrhage
Anastomotic haemorrhage	Exsanguination	Hepatic haematoma	Pancreatic haemorrhage	Spinal epidural haemorrhage
Anastomotic ulcer haemorrhage	Extradural haematoma	Hepatic haemorrhage	Pancreatitis haemorrhagic	Spinal haematoma
Aneurysm ruptured	Extravasation blood	Hereditary haemorrhagic telangiectasia	Papillary muscle haemorrhage	Splenic haematoma
Antepartum haemorrhage	Eye haemorrhage	Hyphaema	Parathyroid haemorrhage	Splenic haemorrhage
Aortic aneurysm rupture	Eyelid bleeding	Implant site bruising	Parotid gland haemorrhage	Splinter haemorrhages
Aortic rupture	Foetal-maternal haemorrhage	Implant site haematoma	Pelvic haematoma	Spontaneous haematoma
Application site bleeding	Gastric haemorrhage	Implant site haemorrhage	Pelvic haematoma obstetric	Stomatitis haemorrhagic
Application site bruising	Gastric ulcer haemorrhage	Incision site haematoma	Pelvic haemorrhage	Subarachnoid haemorrhage
Arterial haemorrhage	Gastric ulcer haemorrhage, obstructive	Incision site haemorrhage	Penile haemorrhage	Subarachnoid haemorrhage neonatal
Arteriovenous fistula site haematoma	Gastric ulcer perforation	Increased tendency to bruise	Peptic ulcer haemorrhage	Subcutaneous haematoma
Arteriovenous fistula site haemorrhage	Gastric varices haemorrhage	Induced abortion haemorrhage	Pericardial haemorrhage	Subdural haematoma
Arteriovenous graft site haematoma	Gastritis alcoholic haemorrhagic	Infusion site bruising	Perineal haematoma	Subdural haematoma evacuation
Arteriovenous graft site haemorrhage	Gastritis haemorrhagic	Infusion site haematoma	Periorbital haematoma	Subdural haemorrhage
Auricular haematoma	Gastroduodenal haemorrhage	Infusion site haemorrhage	Perirenal haematoma	Subdural haemorrhage neonatal
Bladder tamponade	Gastroduodenitis haemorrhagic	Injection site bruising	Peritoneal haematoma	Testicular haemorrhage
Bleeding peripartum	Gastrointestinal angiodysplasia haemorrhagic	Injection site haematoma	Peritoneal haemorrhage	Thalamus haemorrhage
Bleeding varicose vein	Gastrointestinal haemorrhage	Injection site haemorrhage	Petechiae	Third stage postpartum haemorrhage
Blood blister	Gastrointestinal ulcer haemorrhage	Intestinal haemorrhage	Pharyngeal haemorrhage	Thoracic haemorrhage
Blood urine	Genital haemorrhage	Intra-abdominal haemorrhage	Pituitary haemorrhage	Thrombocytopenic purpura
Blood urine present	Gingival bleeding	Intracerebral haematoma evacuation	Placenta praevia haemorrhage	Thrombotic thrombocytopenic purpura
Bloody discharge	Graft haemorrhage	Intracranial haematoma	Pleural haemorrhage	Thyroid haemorrhage
Brain stem haemorrhage	Haemarthrosis	Intracranial tumour haemorrhage	Polymenorrhagia	Tongue haematoma
Breast haematoma	Haematemesis	Intraventricular haemorrhage	Post abortion haemorrhage	Tongue haemorrhage
Breast haemorrhage	Haematochezia	Intraventricular haemorrhage neonatal	Post procedural haematoma	Tonsillar haemorrhage
Broad ligament haematoma	Haematoma	Iris haemorrhage	Post procedural haematuria	Tooth socket haemorrhage
Bronchial haemorrhage	Haematoma evacuation	Large intestinal haemorrhage	Post procedural haemorrhage	Tracheal haemorrhage
Carotid aneurysm rupture	Haematoma infection	Large intestinal ulcer	Postmenopausal	Traumatic haematoma

		haemorrhage	haemorrhage	
Catheter site haematoma	Haematomyelia	Laryngeal haemorrhage	Postpartum haemorrhage	Traumatic haemorrhage
Catheter site haemorrhage	Haematosalpinx	Lip haematoma	Premature separation of placenta	Traumatic intracranial haemorrhage
Cephalhaematoma	Haematospermia	Lip haemorrhage	Proctitis haemorrhagic	Tumour haemorrhage
Cerebellar haematoma	Haematotympanum	Lower gastrointestinal haemorrhage	Prostatic haemorrhage	Ulcer haemorrhage
Cerebellar haemorrhage	Haematuria	Majocchi's purpura	Pulmonary alveolar haemorrhage	Umbilical cord haemorrhage
Cerebral aneurysm ruptured syphilitic	Haematuria traumatic	Mallory-Weiss syndrome	Pulmonary haematoma	Umbilical haemorrhage
Cerebral arteriovenous malformation haemorrhagic	Haemobilia	Mediastinal haematoma	Pulmonary haemorrhage	Upper gastrointestinal haemorrhage
Cerebral haematoma	Haemophilic arthropathy	Mediastinal haemorrhage	Puncture site haemorrhage	Ureteric haemorrhage
Cerebral haemorrhage	Haemopneumothorax	Melaena	Purpura	Urethral caruncle haemorrhage
Cerebral haemorrhage foetal	Haemoptysis	Melaena neonatal	Purpura neonatal	Urethral haemorrhage
Cerebral haemorrhage neonatal	Haemorrhage	Meningorrhagia	Purpura senile	Urinary bladder haemorrhage
Cerebral haemorrhage traumatic	Haemorrhage coronary artery	Menometrorrhagia	Putamen haemorrhage	Urogenital haemorrhage
Cervix haematoma uterine	Haemorrhage foetal	Menorrhagia	Rectal haemorrhage	Uterine haematoma
Cervix haemorrhage uterine	Haemorrhage intracranial	Metrorrhagia	Rectal ulcer haemorrhage	Uterine haemorrhage
Choroidal haemorrhage	Haemorrhage neonatal	Mouth haemorrhage	Renal haematoma	Vaginal haematoma
Chronic gastrointestinal bleeding	Haemorrhage subcutaneous	Mucosal haemorrhage	Renal haemorrhage	Vaginal haemorrhage
Ciliary body haemorrhage	Haemorrhage subepidermal	Muscle haemorrhage	Respiratory tract haemorrhage	Varicose vein ruptured
Coital bleeding	Haemorrhage urinary tract	Myocardial haemorrhage	Respiratory tract haemorrhage neonatal	Vascular pseudoaneurysm ruptured
Colonic haematoma	Haemorrhagic anaemia	Naevus haemorrhage	Retinal haemorrhage	Vascular purpura
Conjunctival haemorrhage	Haemorrhagic arteriovenous malformation	Nail bed bleeding	Retinopathy haemorrhagic	Vascular rupture
Corneal bleeding	Haemorrhagic ascites	Nephritis haemorrhagic	Retroperitoneal haematoma	Venous haemorrhage
Cullen's sign	Haemorrhagic cerebral infarction	Nipple exudate bloody	Retroperitoneal haemorrhage	Vessel puncture site haematoma
Cystitis haemorrhagic	Haemorrhagic diathesis	Occult blood positive	Retroplacental haematoma	Vessel puncture site haemorrhage
Diarrhoea haemorrhagic	Haemorrhagic disease of newborn	Ocular retrobulbar haemorrhage	Ruptured cerebral aneurysm	Vitreous haemorrhage
Disseminated intravascular coagulation	Haemorrhagic disorder	Oesophageal haemorrhage	Scleral haemorrhage	Vulval haematoma
Diverticulitis intestinal haemorrhagic	Haemorrhagic infarction	Oesophageal ulcer haemorrhage	Scrotal haematocoele	Vulval haematoma evacuation
Diverticulum intestinal haemorrhagic	Haemorrhagic ovarian cyst	Oesophageal varices haemorrhage	Scrotal haematoma	Vulval haemorrhage
Duodenal ulcer haemorrhage	Haemorrhagic stroke	Oesophagitis haemorrhagic	Shock haemorrhagic	Wound haemorrhage

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/s/

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: July 11, 2007

To: Thomas Laughren, Director,
Division of Psychiatric Products (DPP)

Thru: Dr. Mark Avigan, Director,
Division of Drug Risk Evaluation (DDRE)

From: Jenna Lyndly, R.N., Safety Evaluator
Division of Drug Risk Evaluation (DDRE)

Subject: Urinary Retention and Urinary Hesitation; NME Review Follow-up

Drug Name(s): Duloxetine (Cymbalta)

Application Type/Number: 21-427, 21-733

Applicant/sponsor: Lilly

OSE RCM #: 2007-1096

Verispan is now SDI

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EXECUTIVE SUMMARY

This analysis is in response to follow-up from the March 13, 2007 pilot NME review¹ for duloxetine where the multidisciplinary team identified urinary hesitation/urinary retention as a follow-up issue.

Duloxetine has a facilitatory effect on incontinence by increasing bladder capacity and urethral sphincter muscle activity. As duloxetine is unable to induce sphincter contractions, urinary retention was thought to be unlikely. No reports of urinary retention resulting in hospitalization or catheterization were seen during the duloxetine clinical trials for major depressive disorder, stress urinary incontinence or benign prostatic hypertrophy; or during duloxetine drug interactions studies with desipramine, paroxetine or tolterodine.² However, the AERS post-marketing case series had 26 of 78 cases reporting serious outcomes; with 62% of the serious outcomes in females.³ Of the 26 cases, there were 9 catheterizations, 8 hospitalizations, and 9 cases of hospitalization + catheterization. Seven of the hospitalizations had a primary or secondary diagnosis of urinary retention/hesitation. The quality of the cases in our series is not optimal; however, the number of cases with serious outcomes describing both a temporal relationship (within one week of starting duloxetine) and a positive dechallenge, with/without treatment indicates a potential risk of urinary retention requiring hospitalization and/or catheterization for patients in the general population.

While the postmarketing labeling includes a listing for urinary retention, the current duloxetine labeling does not inform health care providers of the potential serious outcomes seen in postmarketing AERS reports. Therefore, OSE recommends:

- Consider adding cautionary information to the Precautions section concerning duloxetine associated urinary retention that resulted in hospitalization and/or catheterization as seen in the AERS post-marketing cases.
- Consider modifying the venlafaxine label to be consistent with “class labeling” as identified in the duloxetine for urinary hesitation.

1 BACKGROUND

1.1 INTRODUCTION

The FDA is piloting a review process for drugs classified as new molecular entities⁴ (NME). As part of the pilot, duloxetine was selected as the first drug product to undergo the NME review process. The review involves a template (to guide the new review process) which was used by multidisciplinary reviewers from both the Office of Surveillance and Epidemiology (OSE), and the Office of New Drugs (OND).

¹ New Molecular Entity (NME) Postmarketing Evaluation, Duloxetine, March 13, 2007, Section J, Conclusions and Recommendations

² Viktrup et al. Urinary side effects of duloxetine in the treatment of depression and stress urinary incontinence.

³ In this review we are defining serious outcomes as death, hospitalization, life-threatening and catheterization reports without death, hospitalization or life threatening outcomes

⁴ A new molecular entity (NME) means a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act.

On March 13, 2007, OND and OSE brought together a multidisciplinary workgroup to review the safety profile of duloxetine since approval in August of 2004; including clinical trial safety data, post-marketing adverse event data, new data from completed postmarketing commitments, and labeling changes. A portion of the OSE post-marketing review utilized a data mining analysis, drug use, and the top 50 preferred MedDRA⁵ terms reported in AERS⁶ to provide an overview of post-marketing adverse events. The data mining analysis highlighted urinary hesitation as the preferred term with the highest score, an EB05 of 11.⁷ As a result, the multidisciplinary review team identified post-marketing duloxetine adverse event reports of urinary hesitation and urinary retention for further review, in addition to six other areas⁸.

In this analysis we provide a review of post-marketing duloxetine adverse event reports retrieved from the AERS database coded with the preferred terms “urinary hesitation”, and “urinary retention”. Additionally, as agreed at follow-up meetings, OSE will provide separate written analyses of post-marketing cases of bleeding disorders and drug interactions prior to August 1, 2007; as well as a written analysis of duloxetine medication errors. Also, as agreed upon, to facilitate the NME review process, OND (Division of Psychiatric Drug Products) will conduct analyses of post-marketing cases of blindness, loss of consciousness, and falls.

1.2 REGULATORY HISTORY

Duloxetine is classified as a serotonin-norepinephrine reuptake inhibitor (SNRI) and was initially approved in 20, 30 and 60 mg doses for major depressive disorder (MDD) on August 3, 2004 with a trade name of Cymbalta. Another indication was approved on September 3, 2004 when duloxetine was approved for diabetic peripheral neuropathy pain (DPNP); with the third indication of generalized anxiety disorder (GAD) approved on February 23, 2007. In August of 2004, duloxetine was approved in Europe for stress urinary incontinence under the trade name Yentreve; however, due to safety concerns, the FDA has not approved duloxetine for the indication of stress urinary incontinence.

1.3 PRODUCT LABELING⁹

The current labeling addresses urinary hesitation and urinary retention in the following sections:

Under the “*Adverse Events Occurring at an Incidence of 2% or More Among Cymbalta-Treated Patients in Placebo-Controlled Trials*” Section:

Urinary Hesitation

⁵ Medical Dictionary for Regulatory Affairs

⁶ Adverse Event Reporting System - computerized information database designed to support the FDA's post-marketing safety surveillance program

⁷ OSE Post-Marketing Data mining Analysis, Drug: Duloxetine, Marilyn Pitts, February 20, 2007

⁸ The seven areas targeted for follow-up included: Urinary hesitation/retention, bleeding disorders, drug interactions, blindness, loss of consciousness, fall and medication errors

⁹ Drugs@FDA, Cymbalta, NDA 021427, label approved on 02/23/2007

“Cymbalta is in a class of drugs¹⁰ known to affect urethral resistance.¹¹ If symptoms of urinary hesitation develop during treatment with Cymbalta, consideration should be given to the possibility that they might be drug-related.”

Under the “*Other Adverse Events Observed During the Premarketing and Postmarketing Clinical Trial Evaluation of Duloxetine*” section:

Renal and Urinary Disorders —*Infrequent*: dysuria, micturition urgency, nocturia, urinary hesitation, urinary incontinence, urinary retention, urine flow decreased, and urine odor abnormal; *Rare*: nephropathy.

2 METHODS AND MATERIALS

2.1 INTRODUCTION

We utilized adverse event reports retrieved from the AERS database, a listing of non-serious expected adverse events from the sponsor, drug use information from Verispan¹² and an analysis of the AERS database by WebVDME¹³ (data mining tool) as data sources for this review. The sponsor of duloxetine was granted a waiver for non-serious labeled adverse events on February 7, 2005.¹⁴

2.2 DATA MINING

A data mining search of the Adverse Event Reporting System (AERS) database was performed for this analysis using WebVDME 5.2. This method uses the Multi-item Gamma Poisson Shrinker (MGPS)¹⁵⁻¹⁶ algorithm which analyzes the records contained in the AERS database. The algorithm then quantifies reported drug-event associations by producing a set of values or scores which indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting rate of an event for a particular drug relative to all other drugs and events in the database. MGPS also calculates lower and upper 90% confidence limits for the EBGM values, denoted as EB05 and EB95 respectively.

On January 3, 2007, we queried WebVDME by using the Ingredient (S) run with the search criteria of duloxetine and all reports with an EB05¹⁶ score ≥ 2 , which indicates 95% confidence that the event was reported at least twice as often for duloxetine when compared to all other drugs in AERS. The result of the overall query is provided in a separate OSE document.¹⁷

¹⁰ Selective serotonin-norepinephrine reuptake inhibitors (SNRIs); currently includes duloxetine and venlafaxine

¹¹ The venlafaxine label includes “urinary retention” and “urination impaired”, but not urinary hesitation; Drugs@FDA, Effexor, NDA 020151, label approved on 02/07/2007

¹² Verispan, LLC: Total Patient Tracker, Aug04-Dec06, Extracted Feb07. Files: TPT Cymbalta AUG04-DEC06 Aggregate Product Brand Report.xls, TPT Cymbalta aug04-dec06 Aggregate Gender Report.xls

¹³ Developed by Lincoln Technologies, Inc. in cooperation with the FDA

¹⁴ The non-serious labeled reports of urinary hesitancy and urinary retention are most likely under-represented in the AERS database, and consequently under-represented in WebVDME.

¹⁵ DuMouchel W, Pregibon D. Empirical bayes screening for multi-item associations. Proceedings of the conference on knowledge discovery and data; 2001 Aug 26-9; San Diego, Ca: ACM Press:67-76.

¹⁶ Szarfman A, Machado SG, O'Neill RT. Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. Drug Safety 2002;25:381-92.

¹⁷ OSE Post-Marketing Data mining Analysis, Drug: Duloxetine, Marilyn Pitts, February 20, 2007

2.3 AERS SELECTION OF CASES

We queried the AERS database as follows:

Table 1. AERS Search Strategy

SEARCH INFORMATION	
Source Database	Adverse Event Reporting System (AERS)
Date of Search	March 26, 2007
Drug Name Search Terms	Duloxetine active ingredient and related verbatim terms
MedDRA Adverse Event Search Terms	Urinary Retention, Urinary Hesitation
Search Level	Preferred Terms (PT)

We also requested the sponsor to submit the non-serious labeled event reports of urinary hesitation and urinary retention affected by the existing waiver.

2.4 LITERATURE SEARCH

We searched STAT!REF¹⁸ for definitions of urinary retention and urinary hesitation.

We searched PubMed to determine current information regarding the potential mechanism for duloxetine to effect incontinence with the terms ‘duloxetine and mechanism and incontinence’ with two pertinent articles identified.¹⁹

We searched PubMed for urinary retention and duloxetine. The results were one article which addressed the mechanism of action of duloxetine, the incidence of urinary retention, and examined urinary retention in three duloxetine clinical studies and three drug interaction studies.²⁰

We also searched PubMed with the search terms of ‘urinary retention and prevalence’, ‘urinary retention and incidence’, and ‘urinary retention and epidemiology’ to determine the epidemiology of urinary retention. Three relevant articles and one abstract not available in English were present in all three searches.²¹ An additional search for ‘urinary retention and incidence’ limited to ‘females and humans’ was performed to identify the epidemiology of urinary retention in females. One relevant article was identified.²²

¹⁸ STAT!Ref is an electronic resource for healthcare professionals – www.STAT!Ref.com

¹⁹Schuessler, B. What do we know about duloxetine’s mode of action? Evidence from animals to humans, Jost, W and Marsalek. Duloxetine: mechanism of action at the lower urinary tract and Onuf’s nucleus

²⁰ Viktrup et al. Urinary side effects of duloxetine in the treatment of depression and stress urinary incontinence

²¹ Cathcart et al. Incidence of primary and recurrent acute urinary retention between 1998 and 2003 in England, Meigs et al Incidence rates and risk factors for acute urinary retention: the health professional follow-up study, Verhamme et al. Low incidence of acute urinary retention in the general male population: the triumph project, Abstract - Shimizu, N. Clinical study of acute urinary retention.

²² Kavia et al. Urinary retention in women: its causes and management

An additional search was performed in both PubMed and Google in an attempt to identify any publications or information regarding SNRIs and urinary retention. ‘SNRI and urinary retention’ and ‘selective serotonin and norepinephrine-reuptake inhibitors and urinary retention’ were used as search terms and did not result in any applicable publications.

3 RESULTS

3.1 DATA MINING

The data mining results relevant to urinary hesitation and urinary retention are presented in Table 2 below:

Table 2. Data Mining Results²³ of AERS Cases of Urinary Retention/Hesitation from Marketing to January 3, 2007

DATA MINING RESULTS				
MedDRA Preferred Term	N²⁴	EB05²⁵	EBGM	EB95
Urinary hesitation	32	11.54	15.763	21.011
Urinary retention	55	2.847	3.568	4.426

3.2 AERS CASE SERIES

Case Series (78):

Our search of the AERS database on March 26, 2007 retrieved 84 reports, 78 of which comprise the case series. We excluded six reports from further analysis.²⁶ The overall characteristics of the included cases are detailed in table 3 below:

Table 3: Overall Characteristics of Unique AERS Cases of Urinary Retention/Hesitation from Marketing to March 26, 2007 (n=78)

Location	US (68), Foreign (10)
Report Source	Expedited (17), Direct (2), Periodic (59)
Reporter	Consumer (15), Health Care Professional (62), Foreign Study (1)
Gender	Female (42), Male (36)
Age Range	18 to 85 years, median = 53, n = 58
Indications for Use ²⁷	Anxiety (2), Depression/Bipolar/MDD ²⁸ (35), DPNP ²⁹ /Neuropathy (10), Ill-defined disorder (1), Incontinence/ SUI ³⁰ (5), Myoclonus (1), OCD ³¹ (1), Parkinson’s (1), PTSD ³² (1), Unknown (22)

²³ OSE Post-Marketing Data mining Analysis, Drug: Duloxetine, Marilyn Pitts, February 20, 2007

²⁴ The numbers do not represent individual cases as one case may include PT terms for both urinary hesitation and urinary retention and will be represented for both terms.

²⁵ EB05 is the estimated lower 90% confidence limit for the adjusted observed to expected ratio

²⁶ Excluded = duplicates (3), onset of symptoms after discontinuation of duloxetine (3)

²⁷ One case may have more than one indication.

²⁸ Bipolar depression (1), Depression (26), MDD - Major Depressive Disorder (7), Mild depression with various complaints of pain (1),

Table 3: Overall Characteristics of Unique AERS Cases of Urinary Retention/Hesitation from Marketing to March 26, 2007 (n=78)

Peak Daily Dose	median = 60mg, 20mg to 120mg, n = 69
Concomitant Medication Drug Classes ³³ - labeled for urinary retention/hesitation ³⁴	Anticonvulsants (5), Antidepressants (10), Antihistamine drugs (1), Antimuscarinics/antispasmodics (2), Antipsychotics (7), CNS Agents (1), Genitourinary smooth muscle relaxants (4), Opiate agonists (10), None (4), Unknown (28)
Co-morbid Relevant Medical Conditions ³⁵	BPH ³⁶ (2), Diabetes (8), Instrumentation of GU tract (1), Kidney Stones (2) LUTS ³⁷ (17), MS (1), Parkinson's (3), Pelvic radiation (1), Prostatitis (1), Shy bladder (1), STD (1), TURP ³⁸ (1), UTIs (6), Negative history for GU ³⁹ (9), Unknown (28)
Event PT	Urinary retention (46), Urinary hesitation (29), Urinary retention and urinary hesitation (3)
Onset Information	median = 6.5 days, 5 hours to 'more than a year', n = 41
Offset Information	1 to 30 days, median = 6.5 days, n = 6
Outcomes	Death (0), Hospitalization (17), Life-threatening (1)
Catheterizations	18 (9 of the catheterizations overlap with the hospitalizations)
Duloxetine Status	Discontinued (49), Continued (17), Unknown (12)
Dechallenge	Positive with treatment (10), Positive (18), Negative (4)
Rechallenge	Positive (1)

The data included two positive dechallenge cases without confounding from medications or pre-existing LUTS⁴⁰. The narratives for the two cases are detailed below:

ISR # 5011375

A 28 year old male who denied history of urinary tract symptoms or disorders including BPH, and with no concomitant medications, including over-the-counter medications. Prescribed duloxetine 30 mg QD for major depressive disorder and anxiety. Dose increased to 60 mg QD. Experienced urinary hesitation and retention. Duloxetine discontinued after seven days. Symptoms resolved and did not reoccur.

ISR # 4530908

A 50 year old male with a negative history of urinary tract problems, and no concomitant medications, prescribed duloxetine 30 mg QD for mild depression with anxiety components and

²⁹ Diabetic neuropathy (2), Diabetic peripheral neuropathy (1), DPNP - Diabetic Peripheral Neuropathic Pain (2), Neuralgia (1), Neuropathic pain (1), Neuropathy (1), Peripheral neuropathy (1), Reflex sympathetic disease (1)

³⁰ Incontinence (2), SUI - Stress Urinary Incontinence (3)

³¹ OCD - Obsessive Compulsive Disorder

³² PTSD - Post Traumatic Stress Disorder

³³ Drug Classes from AHFS Drug Information (2007)

³⁴ One case may contain multiple medications labeled for urinary retention/urinary hesitation

³⁵ One case may contain multiple co-morbid conditions

³⁶ BPH - Benign Prostatic Hypertrophy

³⁷ LUTS - Lower urinary tract symptoms - Incontinence (8), frequent urination (1), overactive bladder (2), urinary hesitation (1), urination problems at night (1), urinary retention (2), voiding difficulties (1)

³⁸ TURP - Transurethral Resection of the Prostate

³⁹ GU - Genitourinary

⁴⁰ LUTS - Lower urinary tract symptoms

various pain complaints. On Day 3, experienced a little urinary hesitancy. Day 6, hesitancy increased with nocturia. Discontinued duloxetine. Both symptoms resolved within 2 days.

Serious Outcomes - Hospitalizations and/or Catheterizations (26):

Twenty-six (16F/10M) of the AERS cases required hospitalization and/or catheterization; nine catheterization, eight hospitalization, and nine hospitalization with catheterization. As the literature noted that urinary retention in females is “uncommon” or “rare” and reports of urinary retention in the MDD, SUI and BPH clinical trials were predominantly from males, we will separate the cases by gender.^{41,42}

- ***Cases of hospitalization/catheterizations in females (16)***

Sixteen cases were female (16/26, 62%) with a median age of 53 years old (range 35-85, n=15). Six were hospitalized and catheterized; five were hospitalized and five were catheterized. The median time to onset was 7 days with a range of 2-365 days⁴³ (n=8). Two offsets were reported; both catheterized with offsets of 20 and 30 days.

Hospitalizations (11)

Eleven females were hospitalized; two with a primary diagnosis of urinary retention/hesitation, and one with a secondary diagnosis. Nine cases included concomitant medications labeled for urinary retention and/or medical conditions which might increase the risk of urinary retention. Six positive dechallenges with treatment were described.

Table 4: Overall Characteristics of Unique AERS Cases of Female Hospitalizations with/without Catheterization from Marketing to March 26, 2007 (n=11)

Age Range	median = 70, 42 to 85 years, n = 10
Peak Daily Dose	median = 40mg, 20mg to 120mg, n = 10
Indication for Use ⁴⁴	Depression (4), MDD (1), Incontinence(1), SUI (2), Unknown (3)
Concomitant Medication Drug Classes ⁴⁵ - labeled for urinary retention ⁴⁶	Anticonvulsants (2), Antidepressants (3), Antipsychotics (3), CNS Agents (1), Genitourinary smooth muscle relaxants (2), Opiate agonists (2), Unknown (2)
Co-morbid Relevant Medical Conditions ⁴⁷	Diabetes (3), Parkinson's ⁴⁸ (2), UTIs (4), Unknown (1)
Event PT	Urinary retention (8), Urinary hesitation ⁴⁹ (2), Urinary retention and urinary hesitation (1)
Duloxetine Status	Discontinued (9), Continued (2)

⁴¹ Kavia et al: Urinary Retention in women? Its causes and management. BJU International. 2006;Feb;97(2):281-7.

⁴² Viktrup et al. Urinary side effects of duloxetine in the treatment of depression and stress urinary incontinence.

⁴³ 210 days estimated time used for onset of “6-8 month”, 365 days estimated time used for onset “more than a year”

⁴⁴ One case may have more than one indication.

⁴⁵ Drug Classes from AHFS Drug Information (2007)

⁴⁶ One case may contain multiple medications labeled for urinary retention/urinary hesitation

⁴⁷ One case may contain multiple co-morbid conditions

⁴⁸ Parkinson's (1), possible atypical Parkinson's (1)

⁴⁹ ISR #520371: urinary hesitation described as “could not pee”

Table 4: Overall Characteristics of Unique AERS Cases of Female Hospitalizations with/without Catheterization from Marketing to March 26, 2007 (n=11)

Symptom Resolution	Recovered/recovering (7), Continued (1), Unknown (3)
Positive Dechallenges	(6)
Catheterizations	(6)

The two females hospitalized with a primary diagnosis of urinary retention/hesitation were also treated for overactive bladder with oxybutynin and detail a possible drug interaction. One discontinued oxybutynin; the other discontinued duloxetine, with both reporting resolution of symptoms. The cases are summarized below:

ISR #5034786

Female of unknown age with history of diabetes prescribed duloxetine 20 mg QD. Concomitant medications: insulin, hydrocodone/acetaminophen, oxybutynin, lisinopril, simvastatin and fluoxetine. Increased to 100 mg QD over 3 weeks. Experienced urinary hesitancy. Date of onset unknown. Duloxetine decreased to 60 mg QD. Presented to ER with inability to void. Admitted. Foley inserted for 1 week. Duloxetine discontinued. Symptoms resolved after 1 month.

ISR #5203711

45 year old female with history of diabetes prescribed duloxetine 30 mg BID for depression (b) (6) prescribed oxybutynin, enalapril, zolpidem and naprosyn. Hospitalized for urinary hesitation described as “could not pee.” Oxybutynin discontinued. Discharged from hospital on (b) (6). Retention resolved. Reporter felt that combination of duloxetine with oxybutynin along with history of diabetes caused urinary hesitation.

Catheterizations without hospitalization (5)

Five females were catheterized without hospitalization. Four cases included concomitant medications labeled for urinary retention and/or medical conditions which might increase the risk of urinary retention. Time to onset was reported for four cases with a median of 62 days (range 2-180 days, N=4). One time to offset is reported with a recovery period of 20 days during which self-catheterization and two prescriptions – bethanechol and tamsulosin – were required before resolution of the urinary retention.

Table 6: Overall Characteristics of Unique AERS Cases of Females Catheterized without Hospitalization from Marketing to March 26, 2007 (n=5)

Age Range:	median = 38, 35 to 78 years, n = 5
Peak Daily Dose:	median = 30mg, 30mg to 60mg, n = 5
Indication for Use: ⁵⁰	Depression (1), DPNP (1), MDD (1), Neuralgia(1), Reflex sympathetic disease (1), Unknown (1)
Concomitant Medication Drug Classes ⁵¹ - labeled for urinary retention ⁵²	Antipsychotic (1), Opiate agonists (1), Unknown (3)

⁵⁰ One case may have more than one indication.

⁵¹ Drug Classes from AHFS Drug Information (2007)

⁵² One case may contain multiple medications labeled for urinary retention/urinary hesitation

Table 6: Overall Characteristics of Unique AERS Cases of Females Catheterized without Hospitalization from Marketing to March 26, 2007 (n=5)

Co-morbid Relevant Medical Conditions ⁵³	Diabetes (1), Pelvic surgery and radiation (1), Shy bladder (1), UTI (1), Unknown (0)
Event PT	Urinary retention (5)
Duloxetine Status	Discontinued (3), Continued (1), Unknown (1)
Symptom Resolution	Recovered/recovering (2), Continued (1), Unknown (2)
Positive Dechallenge	(2)

- ***Cases of hospitalization/catheterizations in males (10)***

The ten males (10/26, 38%) had a median age of 68.5 years and a range of 33-83 (n=8). Four were catheterized, three hospitalized and three were hospitalized and catheterized. Median time to onset was 21.5 days with a range of 3-89 days (n=6). Offset information is provided for one case; a hospitalization without catheterization with resolution of urinary retention within 24 hours after discontinuation of duloxetine.

Hospitalizations of male patients (6)

Six males were hospitalized; four with a primary or secondary diagnosis of urinary retention. Five cases included medications labeled for urinary retention and/or medical conditions which may increase the risk of urinary retention. All six discontinued duloxetine with accounts of two positive dechallenges with treatment.

Table 5: Overall Characteristics of Unique AERS Cases of Male Hospitalizations with/without Catheterization from Marketing to March 26, 2007 (n=6)

Age Range	median = 75, 35 to 83 years, n = 5
Peak Daily Dose	median = 60mg, 30mg to 120mg, n = 5
Indications for Use ⁵⁴	Anxiety (1), Bipolar Depression (1), Depression (1), Diabetic neuropathy (1), DPNP (1), Neuropathy(1), Unknown (0)
Concomitant Medication Drug Classes ⁵⁵ - labeled for urinary retention ⁵⁶	Antidepressants (3), Opiate agonists (2), Unknown (3)
Co-morbid Relevant Medical Conditions ⁵⁷	BPH (1), Diabetes (2), Unknown (2)
Event PT	Urinary retention (6)
Duloxetine Status	Discontinued (6)
Symptom Resolution	Recovered/recovering (2), Continued (1), Unknown (3)
Positive Dechallenge	(2)

⁵³ One case may contain multiple co-morbid conditions

⁵⁴ One case may have more than one indication.

⁵⁵ Drug Classes from AHFS Drug Information (2007)

⁵⁶ One case may contain multiple medications labeled for urinary retention/urinary hesitation

⁵⁷ One case may contain multiple co-morbid conditions

Table 5: Overall Characteristics of Unique AERS Cases of Male Hospitalizations with/without Catheterization from Marketing to March 26, 2007 (n=6)

Catheterizations:	(3)
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One positive dechallenge with treatment is summarized below:

ISR # 4539855

35 year old male prescribed duloxetine 60 mg QD for bipolar depression. Urinary retention “almost requiring catheterization.” Duloxetine discontinued. Resolved within 24 hours.

Catheterizations without hospitalization (4)

Three reported concomitant medications labeled for urinary retention and/or medical conditions which may increase the risk of urinary retention. Symptom resolution is reported for two cases; both with descriptions of positive dechallenges with treatment.

Table 7: Overall Characteristics of Unique AERS Cases of Males Catheterized without Hospitalization from Marketing to March 26, 2007 (n=4)

Age Range	median = 65, 33 to 72 years, , n = 3
Peak Daily Dose	median = 60mg, 30mg to 60mg, , n = 3
Indications for Use ⁵⁸	Depression (2), Unknown (2)
Concomitant Medication Drug Classes ⁵⁹ - labeled for urinary retention ⁶⁰	Antipsychotic (1), Opiate agonists (2), Unknown (1)
Co-morbid Relevant Medical Conditions ⁶¹	BPH (1), Kidney stones (1), Prostatitis (1), UTI (1), Unknown (1)
Event PT	Urinary retention (4)
Duloxetine Status	Discontinued (3), Unknown (1)
Symptom Resolution	Recovered/recovering (2), Unknown (2)
Positive Dechallenge	(2)

A positive dechallenge with treatment is summarized below:

ISR #5011384

33 year old male with history of UTI and family history of prostate problems. Prescribed duloxetine 60 mg QD. Three months later, urinary retention. Seen in ER. Catheterized. Results of the catheterization were normal. Diagnosed with “prostate enlarged.” Duloxetine discontinued. Symptoms completely resolved.

Waived Cases (198):

⁵⁸ One case may have more than one indication.

⁵⁹ Drug Classes from AHFS Drug Information (2007)

⁶⁰ One case may contain multiple labeled for urinary retention/urinary hesitation

⁶¹ One case may contain multiple co-morbid conditions

We requested and received from the sponsor a line listing of non-serious labeled waived reports which included 198 domestic cases of urinary retention and/or hesitation.⁶² The line listings consist of 7 fields and provide limited information. The overall characteristics of the cases are detailed in table 4 below:

Table 4: Overall Characteristics of Unique Waived Non-serious Labeled Cases from February 3, 2005 to May 2, 2007, Received from Eli Lilly Inc (n=198)

Location	US (198)
Gender	Female (74), Male (122), Unknown (2)
Age Range	median = 50, 17 to 87 years, n = 134
Peak daily dose	median = 60, 20-120 mg per day, n = 171
Indications for use	Anxiety (5), ADHD ⁶³ (1), Depression/MDD ⁶⁴ (62), Fibromyalgia (3), Neuralgia/Neuropathy ⁶⁵ (23), Pain (11) ⁶⁶ , Panic disorder (2), Unknown (91)
Event PT ⁶⁷	Urinary hesitation (64), Urinary retention (123), Urinary hesitation/retention (11) ,
Event Outcome	Recovered/Recovering (77), Not recovered (26), Worsened (1), Unknown (94),
Catheterizations	Male (6), Female (6), n = 12

Urinary retention was reported in 134 of the waived cases. We provide information concerning these reports below:

- ***Unique Non-serious Labeled Waived Cases of Urinary Retention in Females from February 3, 2005 to May 2, 2007 (n=51)***

Fifty-one (51/134, 38%) of the urinary retention cases were female with a median age of 45 (range 17-80, n=31) and a median dose of 60 mg (range 20-90, n=44). Nineteen (19/51, 37%) reported improvement or resolution of urinary retention. Six of the female patients reported catheterization with three describing a positive dechallenge (n=3).

- ***Unique Non-serious Labeled Waived Cases of Urinary Retention in Males from February 3, 2005 to May 2, 2007 (n=82)***

Eighty-two (82/134, 56%) of the urinary retention cases were male with a median age of 55 (range 25-87, n=57).⁶⁸ The median dose was 60 mg (range 20-60, n=68). Thirty-three (33/82,

⁶² Waived reports from 02/03/05-05/02/07, submitted 05/25/07

⁶³ Attention deficit/hyperactivity disorder

⁶⁴ Depression (56), MDD (6)

⁶⁵ Neuralgia (6), Neuropathy (9), Diabetic neuropathy (3), Neuropathy peripheral (2), Peripheral sensory neuropathy (1), Radiculitis brachial (1), Trigeminal neuralgia (1),

⁶⁶ Pain (5), Back Pain (2), Bone pain (1), Complex Regional Pain Syndrome (1), Myofascial pain syndrome (1), Pain in extremity (1)

⁶⁷ PT = Preferred Term

⁶⁸ Gender was not reported for one urinary retention waived case.

40%) reported improvement or resolution of urinary retention. Six of the male patients reported catheterization with four describing a positive dechallenge (n=4).

Drug Use

The Duloxetine NME Postmarketing Review performed on March 13, 2007 included drug use information stratified by gender which is summarized in Table 9 below:

Table 9: Duloxetine Drug Use⁶⁹; Total Prescriptions (TRX) Volume by Gender

	Drug Use – TRx % from August 2004 through December 2006
Female	73% (10,198,586/14,016,887)
Male	26% (3,684,624/14,016,887)

3.3 LITERATURE SEARCH RESULTS

Definition of Urinary Hesitation/Retention:

Urinary hesitation or hesitancy is defined by Stedman's Medical Dictionary⁷⁰ as "an involuntary delay or inability in starting the urinary stream." The Merck Manual⁷¹ defines urinary retention ranging from incomplete emptying of the bladder to inability to void, acute or chronic and notes that acute urinary retention may be accompanied by pain.

Proposed Mechanism of Duloxetine on Bladder Function:

We reviewed three articles describing the proposed mechanism of duloxetine on bladder functions.

Jost and Marsalek⁷² noted duloxetine was shown to exhibit a dose dependent five fold increase in bladder capacity and eight fold increase in striated urethral sphincter muscle activity in the cat model. The increased striated muscle is the result of inhibiting reuptake of both serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine at Onuf's nucleus in the pudendal nerve; thus increasing striated muscle contraction in the urethral sphincter. Jost and Marsalek's proposed mechanism for the increase in bladder capacity was central afferent modulation. Phase III human studies showed dose dependent decreases in urinary incontinence episodes and micturition intervals.

Schuessler's article reviewed the animal studies which described a limited modulatory effect of serotonin and norepinephrine with glutamate as the primary neurotransmitter for excitation of the pudendal nerve and sphincter contraction. He noted that in the absence of glutamate, serotonin and 5-HT do not have the ability to induce sphincter contractions; therefore, increased levels of serotonin and norepinephrine would not effect voiding. Human studies by Boy et al and Bump et al were referenced by Schuessler who concluded that human studies confirm the proposed

⁶⁹ Source: Verispan, LLC: Total Patient Tracker, Aug04-Dec06, Extracted Feb07. Files: TPT Cymbalta AUG04-DEC06 Aggregate Product Brand Report.xls, TPT Cymbalta aug04-dec06 Aggregate Gender Report.xls

⁷⁰ Stedman's Medical Dictionary, 2006 Lippincott & Wilkins, through STAT!Ref

⁷¹ Merck Manual of Diagnosis and Therapy, The – 18th Ed. (2006), through STAT!Ref

⁷² Jost W, Marsalek P: Duloxetine: mechanism of action at the lower urinary tract and Onuf's nucleus. Clin Auton Res. 2004 Aug;14(4):220-7.

mechanism from animal studies. The study by Bump et al assessed females at 4 weeks and seven months. Schuessler highlighted the lack of impact on voiding in the human studies and also the five-fold increase in cough activity after seven months seen in one woman which was suggestive of a progressive effect of duloxetine on sphincter activity.⁷³

The final journal article reviewed was by Viktrup et al, Lilly Research Laboratories, which reiterated the same proposed mechanism discussed in the previous articles and reviewed the clinical trials for MDD concluding the risk for urinary obstruction should be “negligible” since 5-HT and norepinephrine enhances sphincter activity during the storage phase but not during micturition phase.

Epidemiology of Urinary Retention:

We reviewed four articles and one abstract related to the epidemiology of urinary retention. Three of the articles discuss urinary retention in men. Meigs et al noted an overall background rate for acute urinary retention in men of approximately 5 to 7/1000 per year. Cathcart and Verhamme saw slightly lower rates while Viktrup et al referred to obstructive voiding difficulties in men as “common”. Shimizu noted that 85% of the patients seen by the department of Urology for acute urinary retention from 1993-2005 were male. Two articles discussed acute urinary retention in females. Kavia stated that urinary retention in women is “not a common complaint” and Viktrup et al described urinary retention as “rare” in females. (see appendix for additional details)

Published duloxetine clinical study review:

Viktrup et al reviewed 3 duloxetine studies and 3 duloxetine drug interaction studies in one article. The article reviewed clinical studies and provided an in-depth analysis of urinary retention reported during the duloxetine clinical trials for MDD, SUI and Benign Prostatic Hyperplasia (BPH). There were a total of 4788 patients (3990F/798M) with 22 (16M/6F) reporting subjective symptoms of urinary retention. We have summarized the case details in a table. (See Appendix)

Females (6)

The females had a median age of 68.5 years (range 33-83, n=6). Three patients received a dose of 80mg daily, and three received a dose between 80 and 120mg daily. The median time to onset was 2.5 days with a range of 1-175 days (n=6). Two reported concomitant medications or medical conditions which may increase the risk of urinary retention. One case discontinued duloxetine during the study due to urinary retention. A positive dechallenge occurred for one case when duloxetine was discontinued at the end of the study; the patient had remained on duloxetine for 57 days, while experiencing urinary retention during the treatment time. When the study ended the patient’s urinary retention resolved within one day.

Males (16)

The 16 males had a median age of 53.5 years (range 35-85, n=16); a median time to onset of 8.5 days (range 1-117 days, n=16) and a median time of offset of 1.5 days (range 1-8 days, n=4). The patients received doses ranging from 30 to 120mg daily. Nine cases detailed medical

⁷³ Schuessler B: What do we know about duloxetine’s mode of action? Evidence from animals to humans. BJOG. 2006 MAY;113 Suppl 1:5-9.

conditions and/or concomitant medications which may increase the risk of urinary retention. Four positive dechallenges were noted; one who discontinued during the study due to urinary retention symptoms and three with resolution of symptoms when the study ended and duloxetine was discontinued.

Drug Interaction Studies:

Viktrup et al also reviewed three studies of potential drug interactions with duloxetine with desipramine, a tricyclic antidepressant, paroxetine, a selective serotonin reuptake inhibitor and tolterodine, an antimuscarinic agent. The three studies did not result in reports of urinary retention in the “healthy subjects”. But Viktrup et al noted that caution should be used with any agent such as duloxetine with “the potential to induce or exacerbate an obstructive voiding symptom.”⁷⁴

4 DISCUSSION

4.1 DATA MINING

We utilized data mining, which scores drug-event combinations based on disproportional analysis comparing a drug-event against the AERS database. An elevated score does not imply or prove causality, or an increased relative risk of the event for that drug. Because AERS is a spontaneous adverse events reporting system and confounding is not evaluated prior to inclusion in the database, the actual risk for a drug-event cannot be determined from data mining. Data mining provides a signal which must be further investigated. Additionally, the sponsor was granted a waiver for non-serious, labeled adverse events such as urinary hesitation and urinary retention. As such, in respect to urinary retention and urinary hesitation, the AERS database and data mining are under-represented, as confirmed by the additional 198 non-serious cases submitted from the sponsor’s database.

Even with the under-representation of the waived reports, data mining for duloxetine still showed at least a greater than 2-fold increase in both urinary retention and urinary hesitation with a 95% confidence interval.

4.2 AERS CASE SERIES CHARACTERISTICS

A total of 276 post-marketing reports are included in our review; 78 from AERS and 198 waived reports received from the sponsor. Urinary retention was reported in 169 cases, urinary hesitation in 93 and both urinary retention and urinary hesitation in 14. Of the 276 reports, 116 were female (42%), 158 male (57%).⁷⁵ The males had a median age of 55 (range 21-87, n=111) compared to the females (median 45.5, range 17-85, n=82). The median dose was 60 mg with a range of 20-120 mg (n=69). The median time to onset was 6.5 days with a range of 5 hours to more than a year (n=41). Forty nine discontinued duloxetine with 18 positive dechallenges and one positive rechallenge. The median time to offset was 6.5 days, (range 1 to 30 days, n=6).

⁷⁴ Viktrup et al, p. 73.

⁷⁵ Gender was not reported for 2 cases.

The data included two positive dechallenge cases without confounding from medications or co-morbid medical conditions.

The postmarketing AERS case series included 26 cases with serious outcomes. We include in this definition cases reporting death, hospitalization, life-threatening outcomes, with or without catheterization; as well as catheterization cases that did not report death, hospitalization and/or life-threatening outcomes. There were no death cases; however, eight were hospitalized, nine catheterized, and nine hospitalized and catheterized. Seven of the hospitalizations had a primary or secondary diagnosis of urinary retention/hesitation. In the AERS reports more females (16/26) than males (10/26) had serious outcomes. Twenty of the twenty-six cases included medical conditions and/or medications which may potentially increase the risk for urinary retention.

The females had a median age of 53 years old (range 35-85, n=15); with a median time to onset of 7 days, with a range of 2-365 days⁷⁶ (n=8). The median peak daily dose for the hospitalized and/or catheterized females was 40 mg (range 20-120); while the median in females catheterized without hospitalization was 30 mg (range 30-60); both lower than the median of 60 mg for the AERS case series. Thirteen of the sixteen (81%) included concomitant medications and/or medical conditions which might increase the risk of urinary retention. Eight positive dechallenges with treatment were described among the 11 (73%) reporting symptom resolution. Two females reported offsets; both catheterized with offsets of 20 and 30 days.

The males had a median age of 68.5 years and a range of 33-83 (n=8); with a median time to onset approximately three times longer than the females at 21.5 days, (range of 3-89 days, n=6). The hospitalized and/or catheterized males had a median peak daily dose of 60 mg (range 30-120); the same as the median in the males catheterized without hospitalization (range 20-120) and the case series median. Eight of ten (80%) reported concomitant medications, or medical conditions which might increase the risk of urinary retention. Offset information was provided for one case with resolution in one day. Four of the five reporting symptom resolution described positive dechallenges with treatment.

In addition, twelve catheterizations (6F/6M) were included in the 198 waived reports received from the sponsor with 3 females and 4 males detailing positive dechallenges (n=7).

4.3 LITERATURE SEARCH

The literature describes a mechanism of action of duloxetine for a dose-dependent increase in urinary sphincter activity that has been demonstrated in the cat model. Also noted in cats is a proposed potential mechanism for the dose-dependent increase in bladder capacity. Studies have shown duloxetine's action to be modulatory as duloxetine alters neurotransmitters (serotonin and 5-HT) which are unable to induce sphincter contractions in the absence of glutamate. Human studies have reinforced the mechanisms seen in animal models.

⁷⁶ 210 days estimated time used for onset of "6-8 month", 365 days estimated time used for onset "more than a year"

As duloxetine is unable to induce sphincter contractions, Viktrup et al noted the potential for duloxetine to cause urinary retention was unlikely.⁷⁷ However, reports of urinary retention with positive dechallenges were seen in the clinical trials. Viktrup et al reviewed three duloxetine clinical studies for a total of 4788 patients (3990F/798M) with 22 (16M/6F) reporting subjective symptoms of urinary retention. No reports of acute urinary retention resulting in hospitalization or catheterization were seen. The females had a median age of 68.5 years (range 33-83, n=6). The median time to onset was 2.5 days with a range of 1-175 days. Two (33%) reported concomitant medications or medical conditions which may increase the risk of urinary retention. One of six females (17%) reported a positive dechallenge. The 16 males had a median age of 53.5 years (range 35-85, n=16), a median time to onset of 8.5 days (range 1-117 days, n=16) and a median time of offset of 1.5 days (range 1-8 days, n=4). Nine males (56%) detailed medical conditions and/or concomitant medications which may increase the risk of urinary retention. Four positive dechallenges (25%) were noted by the sixteen males. Viktrup et al determined that BPH, a common risk factor for urinary retention, did not increase the risk for urinary retention during the MDD and BPH duloxetine studies.

Viktrup et al. also reviewed three drug interaction studies with duloxetine. The studies for drug interactions with desipramine, a tricyclic antidepressant, paroxetine, a selective serotonin reuptake inhibitor and tolterodine, an antimuscarinic agent did not result in any reports of urinary retention in “healthy subjects”.

5 CONCLUSION

Voiding is a complex mechanism which is not fully understood. Duloxetine resulted in a dose-dependent eight fold increase in striated sphincter muscle activity in the cat model and was shown to have similar results in human studies. Duloxetine was also shown to have a dose-dependent five fold increase in bladder capacity in cats. In clinical studies, duloxetine demonstrated a dose-dependent decrease in incontinence episodes and a dose dependent increase in time between voids. Duloxetine has been shown to impact urethral closure; however duloxetine’s mechanism of action is considered facilitatory and thus, unlikely to result in urinary retention. Urinary retention with serious outcomes was not seen in the clinical studies. The current duloxetine labeling includes a line listing for urinary retention but does not address urinary retention which results in serious outcomes such as hospitalization or catheterization.

To assess the adequacy of the current labeling, we compared the urinary retention reports from the MDD, SUI and BPH clinical trials with our AERS postmarketing case series. Viktrup et al examined the three clinical studies and noted 22 reports of subjective urinary retention. Viktrup’s review did not include any reports of urinary retention which required catheterization or hospitalization. They determined it unlikely that duloxetine would result in objective urinary retention or retention which would require catheterizations. In comparison, our postmarketing cases series had twenty-six cases with serious outcomes including nine catheterizations, nine catheterizations with hospitalization and eight hospitalizations; with seven of the seventeen hospitalizations having a primary or secondary diagnosis of urinary retention/hesitation.

⁷⁷ Viktrup et al, p 72.

While the clinical studies had roughly the same gender distribution as the postmarketing drug use, with 83% females in the clinical studies and 73% of females in the postmarketing drug use, the AERS postmarketing cases with serious outcomes included more females than males (16F/10M) with eleven females requiring catheterization; compared to Viktrup's urinary retention cases which were predominantly male (16M/6F) and did not result in any serious outcomes. Given the literature describing urinary retention in females as rare or uncommon, we are surprised to see more females than males in our serious outcomes. Our postmarketing females with serious outcomes detailed more positive dechallenges (73%) than Viktrup's urinary retention females (17%). Eighty-one percent of our postmarketing females with serious outcomes reported concomitant medications and/or medical conditions which might increase the potential for urinary retention compared to thirty-three percent in Viktrup's urinary retention cases. Our females described a longer onset (median 7 days) versus Viktrup's median of 2.5 days. Both describe a wide range of onset; 2-365 days in the postmarketing females with serious outcomes; 1-175 days for Viktrup's urinary retention females. One possible explanation for the delayed onset may be the progressive increase on sphincter activity after seven months seen in the Bump study.⁷⁸

In the AERS postmarketing case series, the males with serious outcomes are older; with a median of 68.5 years old in our case series compared to 53 in Viktrup's. Our median time to onset was longer, a median of 21.5 days compared 8.5 days for Viktrup but both had wide ranges; ours with a range of 3-89 days and Viktrup's with a range of 1-117 days. Eighty percent of our males with serious outcomes reported concomitant medications and/or medical histories which may increase the potential for urinary retention compared to 56% of Viktrup's males with urinary retention. Eighty percent of the males with serious outcomes who reported symptom resolution documented a positive dechallenge with treatment; compared to four of 16 (25%) in Viktrup's males with urinary retention.

The quality of the cases in our series is not optimal; however, the cases with serious outcomes with both a temporal relationship to duloxetine, and a positive dechallenge demonstrate a risk of urinary retention resulting in hospitalization and or catheterization for patients using duloxetine. While the current labeling includes a listing of urinary retention, the labeling does not inform health care providers of the serious outcomes seen in our case series.

Health care providers may find the potential for urinary retention resulting in catheterization and/or hospitalization, particularly in female patients, helpful information when considering duloxetine for their patients. In addition, the information concerning the delayed onset of urinary retention seen in both the clinical studies and our postmarketing case series may assist health care providers when assessing duloxetine patients with urinary retention.

RECOMMENDATIONS

- Consider adding cautionary information to the Precautions section concerning duloxetine associated urinary retention that resulted in hospitalization and/or catheterization as seen in the AERS post-marketing cases.

⁷⁸ Schuessler p. 8.

- Consider modifying the venlafaxine label to be consistent with “class labeling” as identified in the duloxetine for urinary hesitation.

Concur,

Marilyn R. Pitts, Pharm.D., Safety Evaluator, Team Leader

Date

cc:

DPP: Hughes/Saini/Glass

OSE: Robinson/Drug File

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APPENDICES

Appendix I: Limitations of AERS

The voluntary or spontaneous reporting of adverse events from health care professionals and consumers in the U.S reflects underreporting and also duplicate reporting. For any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s). The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues. Therefore, counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing drug risk between drugs.

Appendix II: Literature Search Results

Urinary retention was seen predominantly in males (85%) over the 12 year period reviewed by Shimizu et al in the Kinki University Hospital (n=206).⁷⁹ An incidence rate of acute urinary retention for males of 2.2/1000 man years was reported by Verhamme et al following a retrospective cohort study in the Netherlands. (n=56,958)⁸⁰ A prospective cohort study of male health professionals was performed by Meigs et al who calculated a crude incidence of 5.2/1000 person-years and an adjusted incidence of 4.5/1000 person-years with reports of 82 catheterizations in 6,100 men⁸¹; consistent with studies of similar populations such as the Olmstead County study. The incidence increased with age. Calcium channel blockers, beta blockers, nondiuretic antihypertensive and antiarrhythmia medications were accompanied by a 2-3 fold increased risk. A diagnosis of BPH or pre-existing lower urinary tract symptoms was also associated with an increased risk of acute urinary retention. There was no association between clinical risk factors such as smoking, diabetes, or hypertension and an increased risk. Cathcart et al. found an incidence rate of 3.06/1000 men yearly.⁸² While there are several studies on the epidemiology of urinary retention in males, we were unable to find similar population based studies in women. Kavia et al described urinary retention in women as “not a common complaint”.⁸³ Viktrup et al noted that urinary retention in women is “usually related to pharmaceutical agents”, genital organ prolapse, multiple sclerosis (MS), Parkinson’s disease, Diabetes Mellitus or vessico-urethral sphincter dyssynergia. Benign Prostatic Hypertrophy (BPH), prostatic cancer were listed as unique risk factors for the common obstructive voiding symptoms in men along with pharmaceuticals and the same neurologic disorders which pose a risk for females.⁸⁴

Adverse events reported during duloxetine clinical trials for MDD, SUI and Benign Prostatic Hyperplasia (BPH) were reviewed by Viktrup et al; a total of 4788 patients (3990F/798M) (see table 1) with 22 reporting subjective symptoms of urinary retention (female=6, male=16). The MDD trial was comprised of 8 double-blind 8-9 week placebo-controlled studies with 1139 patients (age 18-77, 761F/378M); followed by an open-label study with 1279 enrolled (age18-87, 928F/351M). Patients received duloxetine at doses from 40-120mg with a median duration of 91 days; 41.1% with a duration of more than 180 days. Gender was not provided.

⁷⁹ Shimizu et al: Clinical Study of Acute Urinary Retention. Nippon Hinyokika Gakkai Zasshi. 2006 Nov;97(7):839-43.

⁸⁰ Verhamme et al: Low incidence of acute urinary retention in the general male population: the triumph project. European Urology. 2005 Apr;47(4):494-8.

⁸¹ Excluded history of acute urinary retention and/or TURP. Meigs et al. p 377.

⁸² Cathcart et al: Incidence of Primary and recurrent Acute Urinary Retention Between 1998 and 2003 in England. Journal of Urology. 2006 Jul;176(1):200-4.

⁸³ Kavia et al: Urinary Retention in women? Its causes and management. BJU International. 2006;Feb;97(2):281-7.

⁸⁴ Viktrup et al: Urinary Side Effects of Duloxetine in the Treatment of Depression and Stress Urinary Incontinence, Prim Care Companion J Clin Psychiatry. 2004;6(2):65-79.

The SUI study included 4 double-blind placebo-controlled studies and 4 open-label studies (age 20-87) with longer exposures to duloxetine 40 mg b.i.d.; 191 having more than 12 months of exposure and 818 more than 6 months of exposure; (n=2301). Sixty-nine men with pre-existing symptoms of obstruction were subjects in the BPH placebo-controlled study receiving 30-40 mg of duloxetine for 4-8 weeks. The BPH study included 69 men who had documented mild to moderate obstruction during uroflowmetry, irritative symptoms such as frequency, nocturia or urgency and were either currently in medical therapy for BPH or were a candidate for therapy. Two of the sixty-nine reported urinary retention during the study; one with retention symptoms resulting in discontinuation of duloxetine after the second episode of urinary retention. Per Viktrup et al, a history of BPH or other prostate conditions did not appear to increase subjective symptoms of urinary retention. Viktrup et al concluded obstructive voiding symptoms occurred significantly more often with duloxetine – 1% versus placebo 0.4% (p<.05). While the MDD, SUI and BPH studies included 4788 patients (3990F/798M) with 22 reporting urinary retention symptoms, none of the subjects were catheterized or hospitalized due to urinary retention. Viktrup et al concluded the risk for duloxetine associated urinary retention was limited as was the likelihood of discontinuation due to obstructive voiding symptoms.

Table 1. Abstracted Data from Urinary Retention/Urinary Hesitation in MDD, SUI and BPH Clinical Trials

Action	MDD placebo (n=1139)	MDD Open- label (n = 1279)	SUI placebo (n = 1913)	SUI Open- label (n=1877 ⁸⁵)	BPH placebo (n = 69)	Total n = 4788 (3990F/798M)
Reported Urinary Retention	4 1 F - 0.1% 3M – 0.8%	14 3F -0.3% 11M – 3.2%	0	2F – 0.1%	2M– 2.8%	22 – 0.5% 6 F 16 M
Reported Urinary Hesitation	5 ⁸⁶	1 ⁸⁷	2F	3F	NA ⁸⁸	11
Discontinued due to urinary symptoms	0	2M	0	1F	1M	4 (3M/1F)

Viktrup et al also reviewed studies of potential drug interactions with duloxetine. Small studies for drug interactions with desipramine (n=7), a tricyclic antidepressant, paroxetine (n=12, duration 5 days), a selective serotonin reuptake inhibitor and tolterodine (n=16, duration 5 days), an antimuscarinic agent, did not result in any reports of urinary retention in healthy subjects. But Viktrup et al noted that caution should be used with any agent such as duloxetine with “the potential to induce or exacerbate an obstructive voiding symptom.”⁸⁹

Table 2. Summary of Characteristics for Clinical Trial Subjects Report Urinary Retention

Study	Age	Gender	Total Daily Dose	Onset in Days	Offset in Days	Duration in Days	Discontinued due to retention	Positive Dechallenge	Relevant History
MDD	56	f	80	1	1	57		Y	Pseudoephedrine
MDD	41	f	*80-120	2	35 while on duloxetine	34			
MDD	42	f	*80-120	8	17 while on duloxetine	10			Diabetes
MDD	60	f	*80-120	1	8 while on duloxetine	8			

⁸⁵ 3 open-label studies extensions of placebo-controlled studies. 1 open label study (n = 658) not preceded by placebo controlled study.

⁸⁶ Gender not available in Viktrup et al

⁸⁷ Gender not available in Viktrup et al

⁸⁸ Known obstructive voiding symptoms, Viktrup et al, p 71.

⁸⁹ Viktrup et al, p. 73.

Study	Age	Gender	Total Daily Dose	Onset in Days	Offset in Days	Duration in Days	Discontinued due to retention	Positive Dechallenge	Relevant History
SUI	29	f	80	175	Continued after dc	>50	Y		
SUI	83	f	80	3	Continued after dc	>40			
MDD	28	m	40	8	Continued after dc	>70			Urinary hesitation, decreased urinary flow
MDD	52	m	80	3	26 while on duloxetine	24			
MDD	63	m	120	1	72 while on duloxetine	24			
MDD	59	m	*80-120	15	2	352		Y	Pygeum africanum
MDD	46	m	*80-120	14	182 while on duloxetine	169			Multiple pain meds
MDD	30	m	*80-120	117	362 while on duloxetine	247			
MDD	44	m	*80-120	1	1	10		Y	
MDD	57	m	*80-120	3	Continued after dc	>320			Dysuria, burning on urination
MDD	50	m	*80-120	2	102 while on duloxetine	101			
MDD	62	m	*80-120	9	13 while on duloxetine	5			Polyuria
MDD	58	m	*80-120	1	Continued after dc	>91	Y		Dysuria, shrinkage of urinary canal, pollakiuria, nocturia
MDD	46	m	*80-120	15	Continued after dc	>212			
MDD	47	m	*80-120	23	116 while on duloxetine	94			
MDD	65	m	*80-120	2	Continued after dc	12	Y		Diabetes
BPH	55	m	30	11	8	25		Y	Diabetes, BPH
BPH	62	m	30	17	1	3	Y	Y	BPH

*S Specific prescribed dose unavailable. Open-label extension study with 80-120 mg QD.

Appendix III: Line Listing of Waived Reports

Table 3: Line Listing of Waived Reports of Urinary Retention and Urinary Hesitation from 02/03/05-05/02/07, Submitted by Eli Lilly, Inc, submitted 05/25/07

Manufacturer Control Number	Age	Gender	Date of Report	Dose	Indication	Event PT	Event Outcome
USA0509109470	26 Years	Female	05-Oct-2005	30 mg, daily (1/D)	Anxiety	Urinary hesitation	Not Recovered
S200612001169	56 Years	Female	07-Dec-2006	30 mg, each evening	Depression	Urinary hesitation	Not Recovered
USA0509107492	Unknown	Female	09-Sep-2005	60 mg, daily (1/D)	Fibromyalgia	Urinary hesitation	Not Recovered
USA050597390	69 Years	Female	13-May-2005	60 mg, each evening	Fibromyalgia	Urinary hesitation	Not Recovered
USA050598026	64 Years	Female	23-May-2005	30 mg, each evening	Depression	Urinary hesitation	Recovered
US200610000859	18 Years	Female	05-Oct-2006	30 mg, UNK	Depression	Urinary hesitation	Recovered
USA0511112820	Unknown	Female	05-Nov-2005	30 mg, unknown	Depression	Urinary hesitation	Recovering
USA050495219	38 Years	Female	16-Apr-2005	60 mg, daily (1/D)	Depression	Urinary hesitation	Unknown
USA0507102143	40 Years	Female	13-Jul-2005	60 mg, unknown	Depression	Urinary hesitation	Unknown
USA0507102145	40 Years	Female	13-Jul-2005	60 mg, unknown	Depression	Urinary hesitation	Unknown
US200606002343	25 Years	Female	09-Jun-2006	Unknown	Depression	Urinary hesitation	Unknown
US200605001837	54 Years	Female	09-May-2006	30 mg, UNK	Neuropathy	Urinary hesitation	Unknown
US200512000366	Unknown	Female	02-Dec-2005	20 mg, CAPSULE	Pain	Urinary hesitation	Unknown
USA050598361	45 Years	Female	23-May-2005	20 mg, daily (1/D)	Unknown	Urinary hesitation	Unknown
US200512000359	Unknown	Female	02-Dec-2005	30 mg, CAPSULE	Unknown	Urinary hesitation	Unknown
USA0507103433	42 Years	Female	21-Jul-2005	30 mg, daily (1/D)	Unknown	Urinary hesitation	Unknown
US200607002694	50 Years	Female	17-Jul-2006	30 mg, UNK	Unknown	Urinary hesitation	Unknown
US200607002695	Unknown	Female	17-Jul-2006	30 mg, UNK	Unknown	Urinary hesitation	Unknown
US200602001376	55 Years	Female	07-Feb-2006	60 mg, UNK	Unknown	Urinary hesitation	Unknown
USA050597284	Unknown	Female	11-May-2005	UNK, unknown	Unknown	Urinary hesitation	Unknown
US200607003370	Unknown	Female	19-Jul-2006	Unknown	Unknown	Urinary hesitation, Dysuria	Unknown
USA0507102484	41 Years	Female	18-Jul-2005	60 mg, daily (1/D)	Myofascial pain syndrome	Urinary hesitation, Dysuria	Not Recovered
US200602004323	57 Years	Female	22-Feb-2006	60 mg, daily (1/D)	attention deficit/hyperactivity disorder	Urinary hesitation, Micturition urgency, Urine flow decreased	Not Recovered
US200702003529	Unknown	Female	16-Feb-2007	30 mg, daily (1/D)	Depression	Urinary retention	Not Recovered
US200702005464	57 Years	Female	27-Feb-2007	30 mg, unknown	Depression	Urinary retention	Not Recovered
USA0507102290	Unknown	Female	15-Jul-2005	60 mg, daily (1/D)	Major depression	Urinary retention	Not Recovered
US200701000733	19 Years	Female	04-Jan-2007	30 mg, daily (1/D)	Panic disorder	Urinary retention	Not Recovered
US200607005094	33 Years	Female	28-Jul-2006	30 mg, UNK	Anxiety	Urinary retention	Recovered
US200611000660	43 Years	Female	03-Nov-2006	30 mg, UNK	Anxiety	Urinary retention	Recovered
US200611003378	17 Years	Female	17-Nov-2006	20 mg, daily (1/D)	Depression	Urinary retention	Recovered

Manufacturer Control Number	Age	Gender	Date of Report	Dose	Indication	Event PT	Event Outcome
USA0507102915	48 Years	Female	24-Aug-2005	30 mg, daily (1/D)	Depression	Urinary retention	Recovered
USA050496703	Unknown	Female	04-May-2005	30 mg, daily (1/D)	Depression	Urinary retention	Recovered
US200601005167	40 Years	Female	30-Jan-2006	60 mg, CAPSULE	Depression	Urinary retention	Recovered
US200602004300	55 Years	Female	22-Feb-2006	60 mg, UNK	Depression	Urinary retention	Recovered
USA0507102757	Unknown	Female	21-Jul-2005	60 mg, unknown	Depression	Urinary retention	Recovered
USA0506101574	60 Years	Female	08-Jul-2005	80 mg, daily (1/D)	Depression	Urinary retention	Recovered
US200604001240	65 Years	Female	07-Apr-2006	60 mg, UNK	Neuralgia	Urinary retention	Recovered
USA0506101542	55 Years	Female	07-Jul-2005	30 mg, daily (1/D)	Unknown	Urinary retention	Recovered
USA0507102084	Unknown	Female	14-Jul-2005	30 mg, daily (1/D)	Unknown	Urinary retention	Recovered
US200702002045	18 Years	Female	12-Feb-2007	30 mg, UNK	Unknown	Urinary retention	Recovered
USA050393293	58 Years	Female	24-Mar-2005	30 mg, unknown	Unknown	Urinary retention	Recovered
USA0511112824	80 Years	Female	05-Nov-2005	30 mg, unknown	Unknown	Urinary retention	Recovered
USA050597863	44 Years	Female	16-May-2005	60 mg, unknown	Unknown	Urinary retention	Recovered
US200604004482	79 Years	Female	27-Apr-2006	60 mg, daily (1/D)	Pain in extremity	Urinary retention	Recovering
US200605004422	39 Years	Female	22-May-2006	30 mg, each evening	Trigeminal neuralgia	Urinary retention	Recovering
USA0507102394	Unknown	Female	14-Jul-2005	60 mg, daily (1/D)	Unknown	Urinary retention	Recovering
US200611004244	48 Years	Female	22-Nov-2006	40 mg, daily (1/D)	Depression	Urinary retention	Unknown
USA050392586	29 Years	Female	15-Mar-2005	60 mg, daily (1/D)	Depression	Urinary retention	Unknown
US200604003907	55 Years	Female	25-Apr-2006	60 mg, UNK	Depression	Urinary retention	Unknown
USA050393437	Unknown	Female	26-Mar-2005	60 mg, unknown	Depression	Urinary retention	Unknown
US200608000940	45 Years	Female	04-Aug-2006	90 mg, UNK	Depression	Urinary retention	Unknown
USA0508105484	57 Years	Female	16-Aug-2005	UNK, unknown	Major depression	Urinary retention	Unknown
US200604001241	68 Years	Female	07-Apr-2006	60 mg, UNK	Neuralgia	Urinary retention	Unknown
US200606001134	Unknown	Female	05-Jun-2006	20 mg, UNK	Unknown	Urinary retention	Unknown
US200609001777	44 Years	Female	08-Sep-2006	30 mg, UNK	Unknown	Urinary retention	Unknown
US_0506118105	38 Years	Female	01-Jun-2005	60 mg, daily (1/D)	Unknown	Urinary retention	Unknown
USA050290450	45 Years	Female	19-Feb-2005	60 mg, daily (1/D)	Unknown	Urinary retention	Unknown
USA0509109559	Unknown	Female	04-Oct-2005	60 mg, daily (1/D)	Unknown	Urinary retention	Unknown
US200704000222	19 Years	Female	02-Apr-2007	60 mg, UNK	Unknown	Urinary retention	Unknown
US200609005529	36 Years	Female	22-Sep-2006	60 mg, UNK	Unknown	Urinary retention	Unknown
US200511000444	Unknown	Female	15-Nov-2005	60 mg, UNK	Unknown	Urinary retention	Unknown
US200605003917	Unknown	Female	18-May-2006	60 mg, UNK	Unknown	Urinary retention	Unknown
US200606001394	Unknown	Female	06-Jun-2006	60 mg, UNK	Unknown	Urinary retention	Unknown

Manufacturer Control Number	Age	Gender	Date of Report	Dose	Indication	Event PT	Event Outcome
US200609005062	Unknown	Female	21-Sep-2006	60 mg, UNK	Unknown	Urinary retention	Unknown
USA0510110897	23 Years	Female	18-Oct-2005	60 mg, unknown	Unknown	Urinary retention	Unknown
US_0503114496	49 Years	Female	22-Mar-2005	60 mg, unknown	Unknown	Urinary retention	Unknown
USA0509108508	Unknown	Female	27-Sep-2005	90 mg, unknown	Unknown	Urinary retention	Unknown
US200611002621	78 Years	Female	14-Nov-2006	UNK mg, UNK	Unknown	Urinary retention	Unknown
USA050189379	Unknown	Female	11-Feb-2005	UNK, unknown	Unknown	Urinary retention	Unknown
USA050291000	Unknown	Female	25-Feb-2005	UNK, unknown	Unknown	Urinary retention	Unknown
USA050495117	Unknown	Female	14-Apr-2005	UNK, unknown	Unknown	Urinary retention	Unknown
USA0506101677	Unknown	Female	08-Jul-2005	UNK, unknown	Unknown	Urinary retention	Unknown
USA0509108509	Unknown	Female	27-Sep-2005	UNK, unknown	Unknown	Urinary retention	Unknown
USA0507101964	Unknown	Female	13-Jul-2005	60 mg, daily (1/D)	Unknown	Urinary retention, Urinary hesitation	Not Recovered
US200611003172	Unknown	Male	16-Nov-2006	120 mg, daily (1/D)	Major depression	Urinary hesitation	Not Recovered
US200603004373	59 Years	Male	16-Mar-2006	120 mg, UNK	Neuralgia	Urinary hesitation	Not Recovered
US200611003863	84 Years	Male	21-Nov-2006	30 mg, daily (1/D)	Neuralgia	Urinary hesitation	Not Recovered
USA0508106374	68 Years	Male	26-Aug-2005	60 mg, daily (1/D)	Peripheral sensory neuropathy	Urinary hesitation	Not Recovered
US200602004065	31 Years	Male	21-Feb-2006	30 mg, CAPSULE	Anxiety	Urinary hesitation	Recovered
US200606001156	30 Years	Male	05-Jun-2006	60 mg, UNK	Back pain	Urinary hesitation	Recovered
US200605004217	45 Years	Male	19-May-2006	60 mg, UNK	Back pain	Urinary hesitation	Recovered
USA0508106522	59 Years	Male	29-Aug-2005	30 mg, daily (1/D)	Bone pain	Urinary hesitation	Recovered
US200612004398	61 Years	Male	27-Dec-2006	20 mg, daily (1/D)	Depression	Urinary hesitation	Recovered
US200605000883	36 Years	Male	04-May-2006	60 mg, UNK	Depression	Urinary hesitation	Recovered
US200605006808	44 Years	Male	31-May-2006	60 mg, UNK	Depression	Urinary hesitation	Recovered
USA0507102109	33 Years	Male	14-Jul-2005	60 mg, unknown	Depression	Urinary hesitation	Recovered
US200612001651	21 Years	Male	11-Dec-2006	60 mg, UNK	Pain	Urinary hesitation	Recovered
USA0510111918	62 Years	Male	29-Oct-2005	60 mg, unknown	Pain	Urinary hesitation	Recovered
US200610004710	51 Years	Male	26-Oct-2006	120 mg, UNK	Panic disorder	Urinary hesitation	Recovered
US200701004311	46 Years	Male	23-Jan-2007	30 mg, daily (1/D)	Radiculitis brachial	Urinary hesitation	Recovered
USA0507103055	41 Years	Male	21-Jul-2005	30 mg, daily (1/D)	Unknown	Urinary hesitation	Recovered
US200605003669	50 Years	Male	17-May-2006	60 mg, UNK	Unknown	Urinary hesitation	Recovered
US_0511123661	27 Years	Male	07-Nov-2005	60 mg, unknown	Unknown	Urinary hesitation	Recovered
US200702003397	77 Years	Male	16-Feb-2007	60 mg, unknown	Unknown	Urinary hesitation	Recovered
USA050597356	55 Years	Male	13-May-2005	30 mg, daily (1/D)	Depression	Urinary hesitation	Recovering

Manufacturer Control Number	Age	Gender	Date of Report	Dose	Indication	Event PT	Event Outcome
USA050597578	Unknown	Male	13-May-2005	30 mg, daily (1/D)	Depression	Urinary hesitation	Recovering
US200701005370	Unknown	Male	26-Jan-2007	60 mg, UNK	Unknown	Urinary hesitation	Recovering
US200608004554	32 Years	Male	22-Aug-2006	30 mg, 2/D	Complex regional pain syndrome	Urinary hesitation	Unknown
US200608003595	53 Years	Male	17-Aug-2006	30 mg, daily (1/D)	Depression	Urinary hesitation	Unknown
USA0507102146	30 Years	Male	13-Jul-2005	60 mg, unknown	Depression	Urinary hesitation	Unknown
US_0412109056	53 Years	Male	13-Dec-2004	60 mg, unknown	Depression	Urinary hesitation	Unknown
USA050495611	Unknown	Male	20-Apr-2005	60 mg, unknown	Depression	Urinary hesitation	Unknown
US200605002157	55 Years	Male	10-May-2006	30 mg, UNK	Unknown	Urinary hesitation	Unknown
US200609001795	Unknown	Male	08-Sep-2006	60 mg, daily (1/D)	Unknown	Urinary hesitation	Unknown
US200609002337	21 Years	Male	11-Sep-2006	60 mg, UNK	Unknown	Urinary hesitation	Unknown
US200511000527	50 Years	Male	15-Nov-2005	60 mg, UNK	Unknown	Urinary hesitation	Unknown
US200605000406	Unknown	Male	02-May-2006	60 mg, UNK	Unknown	Urinary hesitation	Unknown
US200611003176	Unknown	Male	16-Nov-2006	Unknown	Unknown	Urinary hesitation	Unknown
USA050188985	Unknown	Male	07-Feb-2005	30 mg, 2/D	Neuropathy	Urinary hesitation, Dysuria	Not Recovered
US200608006336	Unknown	Male	29-Aug-2006	30 mg, daily (1/D)	Depression	Urinary hesitation, Dysuria	Not Recovered
US200606002988	Unknown	Male	13-Jun-2006	60 mg, UNK	Unknown	Urinary hesitation, Dysuria	Unknown
USA0510110777	77 Years	Male	17-Oct-2005	30 mg, unknown	Neuropathy peripheral	Urinary hesitation, Dysuria	Recovered
US200605003650	42 Years	Male	17-May-2006	60 mg, UNK	Unknown	Urinary hesitation, Dysuria	Recovered
US200611002845	52 Years	Male	15-Nov-2006	Unknown	Unknown	Urinary hesitation, Urinary incontinence	Recovered
US200702004967	53 Years	Male	23-Feb-2007	20 mg, UNK	Depression	Urinary retention	Not Recovered
US200612003178	47 Years	Male	18-Dec-2006	30 mg, daily (1/D)	Depression	Urinary retention	Not Recovered
USA0507103807	52 Years	Male	29-Jul-2005	60 mg, daily (1/D)	Depression	Urinary retention	Not Recovered
US200703005406	62 Years	Male	26-Mar-2007	60 mg, daily (1/D)	Depression	Urinary retention	Not Recovered
US200702004105	Unknown	Male	20-Feb-2007	60 mg, unknown	Depression	Urinary retention	Not Recovered
USA050393646	43 Years	Male	30-Mar-2005	UNK, unknown	Depression	Urinary retention	Not Recovered
USA041184374	44 Years	Male	01-Dec-2004	20 mg, 2/D	Anxiety	Urinary retention	Recovered
USA0509108455	87 Years	Male	22-Sep-2005	30 mg, daily (1/D)	Depression	Urinary retention	Recovered
USA0510110268	Unknown	Male	11-Oct-2005	30 mg, daily (1/D)	Depression	Urinary retention	Recovered
US_0501110700	45 Years	Male	20-Jan-2005	30 mg, unknown	Depression	Urinary retention	Recovered
USA0507103144	73 Years	Male	22-Jul-2005	30 mg, unknown	Depression	Urinary retention	Recovered
USA0507101881	60 Years	Male	12-Jul-2005	60 mg, daily (1/D)	Depression	Urinary retention	Recovered
USA0510111687	Unknown	Male	26-Oct-2005	60 mg, daily (1/D)	Depression	Urinary retention	Recovered
USA050291723	67 Years	Male	25-Feb-2005	UNK, unknown	Depression	Urinary retention	Recovered

Manufacturer Control Number	Age	Gender	Date of Report	Dose	Indication	Event PT	Event Outcome
USA050290991	85 Years	Male	25-Feb-2005	UNK, unknown	Depression	Urinary retention	Recovered
USA050597035	38 Years	Male	09-May-2005	60 mg, daily (1/D)	Major depression	Urinary retention	Recovered
US200607004351	Unknown	Male	25-Jul-2006	60 mg, UNK	Major depression	Urinary retention	Recovered
USA0506101113	70 Years	Male	29-Jun-2005	30 mg, daily (1/D)	Neuropathy	Urinary retention	Recovered
US200511002532	50 Years	Male	23-Nov-2005	30 mg, capsule	Unknown	Urinary retention	Recovered
USA0507102913	27 Years	Male	25-Jul-2005	30 mg, daily (1/D)	Unknown	Urinary retention	Recovered
US200704005974	54 Years	Male	26-Apr-2007	30 mg, daily (1/D)	Unknown	Urinary retention	Recovered
US200605005734	70 Years	Male	26-May-2006	30 mg, each evening	Unknown	Urinary retention	Recovered
USA050393296	70 Years	Male	24-Mar-2005	30 mg, unknown	Unknown	Urinary retention	Recovered
USA0507103006	Unknown	Male	22-Jul-2005	30 mg, unknown	Unknown	Urinary retention	Recovered
US200601005285	Unknown	Male	31-Jan-2006	60 mg, UNK	Unknown	Urinary retention	Recovered
USA0508106867	70 Years	Male	01-Sep-2005	60 mg, unknown	Unknown	Urinary retention	Recovered
USA041183340	38 Years	Male	10-Nov-2004	60 mg, daily (1/D)	Depression	Urinary retention	Recovering
US200605002338	65 Years	Male	11-May-2006	60 mg, UNK	Diabetic neuropathy	Urinary retention	Recovering
US200605002339	65 Years	Male	11-May-2006	60 mg, UNK	Diabetic neuropathy	Urinary retention	Recovering
USA050495566	57 Years	Male	19-Apr-2005	60 mg, daily (1/D)	Neuropathy peripheral	Urinary retention	Recovering
US200603005299	73 Years	Male	21-Mar-2006	60 mg, UNK	Unknown	Urinary retention	Recovering
US200611003201	Unknown	Male	16-Nov-2006	60 mg, UNK	Unknown	Urinary retention	Recovering
US200612001539	62 Years	Male	11-Dec-2006	30 mg, UNK	Depression	Urinary retention	Unknown
USA0507103080	40 Years	Male	21-Jul-2005	60 mg, daily (1/D)	Depression	Urinary retention	Unknown
US200604003908	58 Years	Male	25-Apr-2006	60 mg, UNK	Depression	Urinary retention	Unknown
USA0510110430	59 Years	Male	13-Oct-2005	60 mg, unknown	Depression	Urinary retention	Unknown
USA0507102505	Unknown	Male	21-Jul-2005	UNK, unknown	Depression	Urinary retention	Unknown
USA0510109908	50 Years	Male	06-Oct-2005	60 mg, unknown	Diabetic neuropathy	Urinary retention	Unknown
USA0509109451	40 Years	Male	30-Sep-2005	60 mg, unknown	Fibromyalgia	Urinary retention	Unknown
USA050291234	55 Years	Male	01-Mar-2005	60 mg, daily (1/D)	Neuralgia	Urinary retention	Unknown
US200602001094	Unknown	Male	06-Feb-2006	60 mg, UNK	Neuralgia	Urinary retention	Unknown
USA050188877	65 Years	Male	03-Feb-2005	30 mg, unknown	Neuropathy	Urinary retention	Unknown
USA050496062	43 Years	Male	27-Apr-2005	30 mg, daily (1/D)	Unknown	Urinary retention	Unknown
US200603003388	Unknown	Male	14-Mar-2006	30 mg, UNK	Unknown	Urinary retention	Unknown
USA050393504	55 Years	Male	26-Mar-2005	30 mg, unknown	Unknown	Urinary retention	Unknown
USA0506101672	Unknown	Male	07-Jul-2005	30 mg, unknown	Unknown	Urinary retention	Unknown
USA050598701	42 Years	Male	25-May-2005	60 mg, daily (1/D)	Unknown	Urinary retention	Unknown

Manufacturer Control Number	Age	Gender	Date of Report	Dose	Indication	Event PT	Event Outcome
USA050291656	Unknown	Male	04-Mar-2005	60 mg, daily (1/D)	Unknown	Urinary retention	Unknown
US200605004117	40 Years	Male	19-May-2006	60 mg, UNK	Unknown	Urinary retention	Unknown
US200512001838	50 Years	Male	12-Dec-2005	60 mg, UNK	Unknown	Urinary retention	Unknown
US200605003918	Unknown	Male	18-May-2006	60 mg, UNK	Unknown	Urinary retention	Unknown
US200609002950	Unknown	Male	13-Sep-2006	60 mg, UNK	Unknown	Urinary retention	Unknown
USA0509109445	41 Years	Male	30-Sep-2005	60 mg, unknown	Unknown	Urinary retention	Unknown
USA050598688	45 Years	Male	25-May-2005	60 mg, unknown	Unknown	Urinary retention	Unknown
US_0511123830	50 Years	Male	08-Nov-2005	60 mg, unknown	Unknown	Urinary retention	Unknown
USA0508105514	57 Years	Male	17-Aug-2005	60 mg, unknown	Unknown	Urinary retention	Unknown
USA0508105414	65 Years	Male	15-Aug-2005	60 mg, unknown	Unknown	Urinary retention	Unknown
USA0506100284	80 Years	Male	15-Jun-2005	60 mg, unknown	Unknown	Urinary retention	Unknown
USA0509109555	Unknown	Male	04-Oct-2005	60 mg, unknown	Unknown	Urinary retention	Unknown
USA050291255	50 Years	Male	01-Mar-2005	UNK, unknown	Unknown	Urinary retention	Unknown
USA050495029	Unknown	Male	13-Apr-2005	UNK, unknown	Unknown	Urinary retention	Unknown
USA050495537	Unknown	Male	13-Apr-2005	UNK, unknown	Unknown	Urinary retention	Unknown
USA050495546	Unknown	Male	13-Apr-2005	UNK, unknown	Unknown	Urinary retention	Unknown
USA050597042	Unknown	Male	09-May-2005	UNK, unknown	Unknown	Urinary retention	Unknown
USA050598141	Unknown	Male	07-Jul-2005	UNK, unknown	Unknown	Urinary retention	Unknown
USA050598926	Unknown	Male	26-May-2005	UNK, unknown	Unknown	Urinary retention	Unknown
US200512004204	Unknown	Male	28-Dec-2005	Unknown	Unknown	Urinary retention	Unknown
US200612002766	71 Years	Male	15-Dec-2006	30 mg, UNK	Neuropathy	Urinary retention	Worsened
US200702005703	Unknown	Male	28-Feb-2007	60 mg, UNK	Neuropathy	Urinary retention, Micturition urgency	Unknown
US200607001863	67 Years	Male	12-Jul-2006	30 mg, UNK	Pain	Urinary retention, Urinary hesitation	Not Recovered
USA050189300	84 Years	Male	11-Feb-2005	UNK, unknown	Neuropathy	Urinary retention, Urinary hesitation	Not Recovered
USA050393935	48 Years	Male	24-Mar-2005	UNK, unknown	Unknown	Urinary retention, Urinary hesitation	Recovered
USA0508105172	29 Years	Male	12-Aug-2005	60 mg, unknown	Depression	Urinary retention, Dysuria	Recovered
US200601004520	63 Years	Male	26-Jan-2006	20 mg, daily (1/D)	Major depression	Urinary retention, Pollakiuria	Recovered
US200610001591	69 Years	Male	10-Oct-2006	60 mg, UNK	Neuropathy	Urinary retention, Pollakiuria	Not Recovered
US200604001928	56 Years	Male	12-Apr-2006	60 mg, UNK	Neuropathy	Urinary retention, Urinary hesitation	Unknown
US200605003649	70 Years	Male	17-May-2006	60 mg, daily (1/D)	Unknown	Urinary retention, Urinary hesitation	Recovered
USA050495406	Unknown	Male	19-Apr-2005	60 mg, unknown	Unknown	Urinary retention, Urinary hesitation	Recovered

Manufacturer Control Number	Age	Gender	Date of Report	Dose	Indication	Event PT	Event Outcome
USA050393342	48 Years	Male	24-Mar-2005	UNK, unknown	Unknown	Urinary retention, Urinary hesitation	Recovered
USA0507104189	53 Years	Male	02-Aug-2005	30 mg, unknown	Depression	Urinary retention, Urinary hesitation	Unknown
USA050291653	Unknown	Male	04-Mar-2005	60 mg, daily (1/D)	Unknown	Urinary retention, Urinary hesitation	Unknown
USA0510111398	25 Years	Male	21-Oct-2005	30 mg, daily (1/D)	Pain	Urinary retention, Urinary hesitation, Pollakiuria	Recovered
US_0502113494	Unknown	Unknown	28-Feb-2005	30 mg, unknown	Unknown	Urinary hesitation	Unknown
US200702003542	Unknown	Unknown	16-Feb-2007	60 mg, UNK	Depression	Urinary retention	Unknown

Appendix IV: Postmarketing AERS Case Series

Table 4. Included Post-Marketing Cases from AERS, Search Date = 03/26/07

ISR LOC	Medication Status/Medical intervention	Factors which increase strength of signal	Case Summary/Notes	Factors which decrease strength of signal
5034786 US	DC Hospitalized for urinary retention admitted through ER, Cathed	Temporal relationship to duloxetine. Duloxetine dc. Positive dechallenge with treatment.	Female of unknown age with hx of diabetes prescribed duloxetine 20 mg QD. Increased by 20 mg increments up to 100 mg QD over unknown time frame. C/O urinary hesitancy. Duloxetine decreased to 60 mg QD. Presented to ER with c/o inability to void. Admitted. Foley inserted for 1 week. Duloxetine dc. Symptoms resolved after 1 month.	Hx of diabetes. Oxybutynin and fluoxetine labeled for urinary retention; hydrocodone/acetaminophen - opiate agonists may cause urinary retention. Symptoms resolved after 1 month; half life of duloxetine 12 hours. Unclear information regarding date of dc.
5002380 FOR	DC Hospitalized for urinary retention Cathed	Medical confirmation of retention. No previous dx of BPH – new dx. Reported hx neg for UTI and renal failure. Duloxetine dc.	77 yo male prescribed duloxetine 60 mg QD for diabetic polyneuropathy. Developed urinary retention over 2 months. Duloxetine dc. Hospitalized for urinary retention. Cathed. Overflow bladder dx with .5 L residual. Distinctive BPH dx – previously unknown. Symptoms did not improve after 2 weeks without duloxetine. Surgery performed.	Hx of diabetes. New dx: BPH. Symptoms continued after dc and required surgical intervention. Negative dechallenge.
5036331 US	DC/Restarted Hospitalized with acute urinary retention	Duloxetine dc.	62 yo male prescribed duloxetine 60 BID for neuropathy. Hospitalized with acute urinary retention. Duloxetine dc. Prescribed 2 new meds for BPH. Duloxetine restarted. Neurologist and urologist managing patient.	New dx: BPH; Restarted duloxetine. Insufficient information. Concomitant meds, medical hx and symptom resolution not reported.
5145483 5117308 US	DC Hospitalized for hyponatremia and acute urinary retention Cathed	H&P from admission included. Medical confirmation of retention. Hx of incontinence. Rechallenge: With restart, symptoms appear to have increased since cathed after restarted. Symptoms resolving after dc. Positive dechallenge with treatment.	76 yo female with distant hx of UTI and current hx of incontinence. Prescribed duloxetine 30 mg QD. On an unknown date, c/o urinary retention with additional CNS, GI and musculoskeletal complaints. Duloxetine dc. Restarted duloxetine 30. C/O urinary retention. Cathed. Developed UTI. Continued to decline. Duloxetine dc. Hospitalized one day after duloxetine dc for confusion and weakness. Dx – hyponatremia and acute urinary retention. UA – nml. Urine C&S – no growth. Recovering. NOTE: conflicting information regarding hx of retention vs. incontinence.	No information of resolution with first dc. Unclear if catheter removed prior to discharge.
5044966 US	DC Hospitalization for fecal impaction and urinary retention Cathed	Reported hx neg for BPH, urethral stricture, or frequent UTI. Symptoms resolved after dc Positive dechallenge with treatment.	83 yo male prescribed duloxetine 30 mg for depression. No previous hx of BPH. Day 8, hospitalized for urinary retention and fecal impaction. Cathed. Duloxetine dc. Hx of “constipation with many psychotropic drugs.” Symptoms resolved.	Dextropropoxyphene - opiate agonists may cause urinary retention; concurrent dx of fecal impaction.

ISR LOC	Medication Status/Medical intervention	Factors which increase strength of signal	Case Summary/Notes	Factors which decrease strength of signal
5203711 5023132 US	Continued Hospitalized for “urinary hesitation”	Oxybutynin indicated for overactive bladder.	45 yo female with hx of diabetes prescribed duloxetine 30 mg BID for depression. Over 1 year later, hospitalized for c/o urinary “hesitation” described as “could not pee.” Oxybutynin dc. Resolved.	Hx of diabetes. Oxybutynin labeled for urinary retention. Symptoms resolved after oxybutynin dc. Symptoms did not result in dc of duloxetine.
4683860 US	DC Hospitalized for urinary retention	Duloxetine dc. No report of hx of BPH.	Male of unknown age prescribed duloxetine for DPNP. Hospitalized for c/o urinary retention.	Hx of diabetes. Insufficient information. Concomitant meds and symptom resolution not reported
4908994 US	DC Hospitalized for pyelonephritis Cathed	Hx of incontinence. Duloxetine dc. Positive dechallenge with treatment.	78 yo female with hx of frequent UTIs and incontinence. Prescribed duloxetine 20 mg QD for depression. Increased to 60 on unknown date. 6-8 months later hospitalized with pyelonephritis. In hospital, c/o urinary retention. Cathed. Urine C&S – pseudomonas. Duloxetine dc. Resolved.	Hx of UTIs; pseudomonas in urine; concurrent dx of pyelonephritis; aripiprazole labeled for retention;
5177220 US	DC Hospitalized for suicidal ideation Cathed	Duloxetine dc.	75 yo male with hx of BPH. Hospitalized for depression. While hospitalized, prescribed duloxetine 60 mg QD for depression and anxiety. 35 days later hospitalized for suicidal ideation. C/O urinary retention while hospitalized. Cathed. TUR performed approximately 6 weeks after discharge. Duloxetine dc 2.5 weeks after the TUR.	Hx of BPH; required surgical intervention to resolve symptoms. TUR while on duloxetine. Reason for DC not reported. Fluoxetine, sertraline hydrochloride and olanzapine labeled for urinary retention.
5007901 FOR	DC Hospitalization “serotonergic delirium/ serotonine syndrome” Cathed	Medical confirmation of retention. Symptoms resolving after dc. Positive dechallenge with treatment.	79 yo female prescribed duloxetine 30 mg QD for depression. Day 3, hospitalized. Cathed for urinary retention. – 800cc residual. Dx with “serotonergic delirium/serotonine syndrome.” Prolonged hospitalization. Duloxetine dc. Mirtazapine held for 1 week. Recovering.	Reboxetine labeled for urinary retention; concurrent dx of serotonergic delirium/serotonine syndrome.
5152361 FOR	Continued Hospitalized for exacerbation of depressive symptoms Cathed	After dose increase.	44 yo female prescribed duloxetine 60 mg QD for bipolar affective disorder with severe depressive episodes. Hospitalized for exacerbation of depressive symptoms. Olanzapine prescribed. While hospitalized, duloxetine increased to 120 mg QD. Day 3 after dose increase, c/o urinary retention. I&O Cath. Continued to c/o urinary retention intermittently.	olanzapine, gabapentin and aripiprazole labeled for retention. Temporal relationship to olanzapine. Symptoms did not result in dc of duloxetine.
4687690 US	DC Hospitalized for major depressive disorder Cathed	Hx of incontinence; medical confirmation of retention. Duloxetine dc.	53 yo female with hx of urinary incontinence. Prescribed duloxetine 30 mg QD for major depressive disorder. Day 6, UA pos for klebsiella and proteus mirabilis. Day 7, c/o urinary retention. Foley inserted. 1200cc residual. Duloxetine increased to 60 mg QD. Day 8, renal US – R pelvis caliectasis. Duloxetine decreased to 30 mg QD. Day 9, foley dc. Abx prescribed. Day 11, cathed with 1975cc residual. Day 12, phenoxybenzamine prescribed. Day 14 phenoxybenzamine decreased due to incontinence. Day 17, cathed. Day 18, duloxetine dc. Day 21, phenoxybenzamine increased. Bethanechol prescribed. Day 27, UA 3+ bacteria. Abx prescribed. Urology consult.	Underlying UTI; ultram labeled for retention. Insufficient information: symptom resolution not reported.

ISR LOC	Medication Status/Medical intervention	Factors which increase strength of signal	Case Summary/Notes	Factors which decrease strength of signal
4999908 FOR	DC Hospitalized for acute abdomen life threatening	Hx of incontinence. Medical confirmation of retention. Resolved after dc Positive dechallenge with treatment.	STUDY: 81 yo female with hx of UTI. Prescribed duloxetine 20 mg QD for stress incontinence. Day 13, increased to 40 mg QD. Day 15, hospitalized with dx of acute abdomen with subfebrile temperature. US of abdomen – urinary retention and “subileus of small intestine”, liver cyst and inconspicuous abdominal findings. Duloxetine dc. Treated with laxative, food abstention and abx. After treatment, dysuria resolved. US – no urinary retention, UA – nml. Recovered. Note: symptoms occurred after dose increase.	UTI 2 weeks PTA. Concurrent dx of sub-ileus/acute abdomen. Insufficient information: Concomitant meds not reported.
4607585 FOR	DC Hospitalized for depressed level of consciousness	Hx of stress urinary incontinence Medical confirmation of retention. Resolved after dc Positive dechallenge with treatment.	64 yo female prescribed duloxetine 40 mg QD for stress urinary incontinence. On the 5 th day, c/o depressed LOC, unable to eat and drink. Duloxetine dc. Hospitalized with hyponatremia, hypokalemia and dehydration. Diagnosed with urinary retention while hospitalized. Recovered.	Urinary retention reported while hospitalized for treatment of electrolyte imbalance. Insufficient information of treatment provided during hospitalization.
4539855 US	DC Hospitalized for suicidal ideation	Resolved within 24 hours after dc. Positive dechallenge	35 yo male prescribed duloxetine 60 mg QD for bipolar depression. C/O urinary retention “almost requiring urinary catheterization.” Duloxetine dc. Resolved within 24 hours. Hospitalized for suicidal ideation – unknown time. Note: unclear if urinary retention occurred during hospitalization.	Insufficient information: Concomitant meds and medical hx not reported.
4546436 FOR	DC Hospitalized for increased Parkinson ‘s symptoms	Hx of incontinence. Duloxetine dc.	85 yo female with hx of Parkinson’s prescribed duloxetine for urinary incontinence. Day 6 admitted for increased Parkinson’s symptoms. Treated for pneumonia. C/O urinary retention. E. coli in urine. Treated with abx. CLL suspected.	Hx of Parkinson’s. Underlying UTI. Levodopa labeled for urinary retention; Tilidin - Opiate agonists may cause urinary retention. Insufficient information: symptom resolution not reported.
5036025 US	DC Hospitalized with SJS	Duloxetine dc.	42 yo female prescribed duloxetine 60 mg QD. Topiramate increased – time frame unknown. Approximately 4 weeks after first dose of duloxetine, hospitalized with SJS. Also c/o of urinary hesitation with additional GI symptoms, restless leg syndrome and restlessness. Duloxetine dc.	topiramate and bupropion labeled for urinary retention. hydrocodone/acetaminophen - Opiate agonists may cause urinary retention. Insufficient information: symptom resolution not reported. Concurrent dx: SJS.
4877214 US	DC ER Cathed	Duloxetine dc. Positive Dechallenge with treatment.	45 yo female prescribed duloxetine 30 mg QD for DPNP. C/O urinary retention 2 days later. Went to ER. Cathed for urinary retention. Retention resolved. Note: duloxetine dc for increased HR. Date of DC not reported. Unclear if duloxetine dc prior to resolution of urinary retention.	Hx of diabetes. Risperidone labeled for urinary retention. Unclear information regarding dc and resolution of urinary retention.
4531324 US	DC Cathed	Medical confirmation of retention. Duloxetine dc.	Male of unknown age prescribed duloxetine. C/O urinary retention. Cathed – “2300 cc” residual. Duloxetine dc.	Insufficient information. Concomitant meds, med hx and symptom resolution not reported.
5007826 FOR	NR ER Cathed	No previous dx of BPH	72 yo male prescribed olanzapine and duloxetine for depression and bipolar disorder. Day 7, c/o urinary retention. ER. Cathed. Referred to urologist. Possible BPH - still evaluating.	New dx: BPH; olanzapine labeled for urinary retention. Insufficient information: duloxetine status and symptom resolution not reported.

ISR LOC	Medication Status/Medical intervention	Factors which increase strength of signal	Case Summary/Notes	Factors which decrease strength of signal
4533068 US	DC Cathed	Hx negative for urinary retention. Medical confirmation of retention. Duloxetine dc. Positive dechallenge with treatment.	65 yo male with hx of BPH, prostatitis and “urinary problems at night.” Prescribed duloxetine 60 mg QD for depression. On the 3 rd day, c/o urinary retention. Duloxetine dc on the 3 rd day. Day 11, cath with 800cc of residual per urologist. Day 11, prescribed ciprofloxacin and tamsulosin. Recovering.	Hx of BPH and LUTS. Propoxyphene/acetaminophen - opiate agonists may cause urinary retention. Retention continued and worsened. Cathed 8 days after duloxetine dc. Required abx and medication to treat ongoing symptoms after dc of duloxetine. Duloxetine half-life 12 hours.
4683967 US	DC Cathed	Medical confirmation of retention. Duloxetine dc. Positive dechallenge with treatment.	35 yo female with hx of UTI and shy bladder. Meds: phenazopyridine hydrochloride, trimethoprim/sulfamethoxazole. Prescribed duloxetine 30 mg QD for depression. DC duloxetine on day 2. On day 4, cathed with 1000cc residual. Cathed on day 5 with over 1000cc residual. C/O paresthesia and numbness of perineum and perirectum. On day 10, Bethanechol chloride prescribed. Self-cath initiated. On day 13, Foley inserted. Urine C&S neg. Day 16, Foley removed. Unable to void. Day 18, prescribed tamsulosin. Day 20, numbness resolved. Voiding. Self-cath dc.	Hx of UTI and shy bladder. Underlying UTI; required significant medical intervention after dc of duloxetine to treat ongoing retention. Symptoms continued for 16 days after dc. Duloxetine half-life 12 hours.
5049084 US	DC Cathed	Duloxetine dc.	78 yo female with hx of pelvic radiation. Prescribed duloxetine 30 mg QD for DPNP. Approximately 4 months later, c/o urinary retention. Cathed. No flank or suprapubic discomfort/mass. Referred to urologist. Duloxetine dc. Symptoms continued.	Hx of pelvic radiation. Symptoms continued after dc. Negative dechallenge. Insufficient information. Concomitant meds not reported.
4682705 US	NR ER Cathed		38 yo female prescribed duloxetine 60 mg QD. C/O urinary retention. Sent to ER from PCP's office. “Through surgical procedure, the patient had a tube implanted in her bladder.”	Insufficient information. Concomitant meds, duloxetine status and symptom resolution not reported.
5011384 US	DC ER Cathed	No previous dx of BPH. Results of cath - nml. Symptoms completely resolved after dc. Positive Dechallenge.	33 yo male with hx or UTI and family hx of prostate problems. Prescribed duloxetine 60 mg QD. 3 months later, c/o urinary retention. Seen in ER. Cathed. Results of the catheterization were normal. Dx with “prostate enlarged.” Duloxetine DC. Symptoms completely resolved. Note: conflicting information – one report – no meds	New dx: enlarged prostate; Hydrocodone/acetaminophen - opiate agonists may cause urinary retention.
4876289 US	Continued Cathed	Reported neg hx for UTIs.	38 yo female prescribed duloxetine 60 mg for MDD. 6 months later, c/o urinary retention. PE – discomfort in pelvis. Cath – 450ml. duloxetine continued. Retention not resolved. Unwilling to dc duloxetine because it had been so helpful.	6 month onset Concomitant – methadone – opiate agonists may cause retention
4683086 US	DC/Restarted	Temporal relationship to duloxetine. Positive dechallenge/rechallenge Dose response – increased symptoms with increased dose.	46 yo female prescribed duloxetine 30 mg QOD for PTSD. C/O urinary frequency and bladder not emptying. Duloxetine DC. Resolved. Duloxetine 30 mg QOD restarted. Urinary symptoms recurred. Dose increased to 30 mg QD. C/O increased urinary retention/frequency with onset of burning with urination. Also c/o GI, CNS and ocular symptoms after dose increase. Continued duloxetine with continued c/o urinary symptoms.	Concomitant – diphenhydramine -anticholinergic effect may include urinary retention

ISR LOC	Medication Status/Medical intervention	Factors which increase strength of signal	Case Summary/Notes	Factors which decrease strength of signal
4530908 US	DC	No prior hx of any urinary problems. No concomitant meds. Resolved within 48 hours of dc. Positive dechallenge.	50 yo male prescribed duloxetine 30 mg QD for mild depression with anxiety. No prior hx of any urinary problems. No concomitant meds. On the 3 rd day, c/o “a little urinary hesitancy.” On the 6 th day, experienced increased hesitancy and nocturia. Duloxetine dc by MD. Symptoms resolved after 2 days.	
5011375 US	DC	No hx of urinary problems or BPH. No concomitant meds. Resolved after dc and did not reoccur. Positive dechallenge.	28 yo male prescribed 30 mg QD for major depressive disorder and anxiety. No hx of urinary problems or BPH. No concomitant meds. Increased to 60 mg QD. C/O urinary retention and hesitation. Duloxetine dc after 7 days. Symptoms resolved and did not reoccur.	
4532754 US	DC	Temporal relationship to duloxetine. Symptoms resolved by next day. Positive dechallenge.	46 yo female prescribed duloxetine 60 mg QD for depression. Long term use of lasix. C/O urinary retention within 1-2 days. Duloxetine dc within first week. Symptoms resolved by next day.	zolpidem labeled for urinary retention
4533031 US	DC	Temporal relationship to duloxetine. Resolved after dc. Positive Dechallenge	84 yo male with hx of TURP X 2. Prescribed duloxetine 60 mg QD for diabetic peripheral neuropathy. Day 3, c/o urinary hesitation. Day 4, Duloxetine dc. Symptoms resolved.	Hx of TURP X 2. Insufficient information: Concomitant meds not reported.
4938502 FOR	DC	No previous hx. Resolved after dc Positive dechallenge	43 yo male prescribed duloxetine 30 mg QD for depression, increased to 60 mg QD after 1 week. Per MD, no previous micturition problems. After increase, c/o “partial urinary retention” and pain over scrotum. Duloxetine dc. Symptoms resolved after 11 days. Note: Symptoms occurred after dose increase.	Resolution of symptoms took 11 days. Half-life 12 hours.
4653817 US	DC	Unclear information: no hx of BPH. C&S neg. Improved after dc. Positive dechallenge.	75 yo male with hx of BPH, prescribed duloxetine 30 mg QD for depression and anxiety. Also received influenza vaccine. 5 hours after the initial dose of duloxetine, c/o urinary hesitancy and fever, extreme fatigue, sweating and multiple CNS and GI symptoms. Day 2, duloxetine increased to 60 mg QD. Urine C&S neg – date unknown. Day 4, duloxetine dc. Symptoms improved. Note: conflicting information –no hx of BPH vs. hx/concurrent BPH. Constellation of symptoms reported in conjunction with urinary hesitancy.	Unclear information :Hx of BPH Constellation of symptoms including fever
5010058 US	DC	Resolved after dc Positive dechallenge	62 yo male prescribed duloxetine 30 mg QD for depression. C/O urinary retention. Duloxetine dc. Symptoms resolved.	Insufficient information: Concomitant meds not reported.
4771494 US	DC	Resolved after dc Positive dechallenge	78 yo male prescribed duloxetine 60 mg QD. C/O urinary retention. Duloxetine dc. Symptoms abated.	Insufficient information: Concomitant meds not reported.

ISR LOC	Medication Status/Medical intervention	Factors which increase strength of signal	Case Summary/Notes	Factors which decrease strength of signal
4533564 US	DC	? no relevant hx. Symptoms resolved after dc Positive dechallenge	Male of unknown age prescribed duloxetine 30 mg QD for major depressive disorder. Increased to 60 mg QD after unknown time frame. After increase, c/o urinary hesitation. Duloxetine dc “during the second week.” Symptoms resolved. Note: conflicting information – no relevant hx vs. did not ask. symptoms after dose increase	Insufficient information: Concomitant meds not reported.
4532267	DC	No relevant hx. Symptoms resolved after dc Positive dechallenge	Male of unknown age prescribed duloxetine 30 mg QD for major depressive disorder. No relevant hx. Increased to 60 mg QD after unknown time frame. After increase, c/o urinary hesitation. Duloxetine dc “during the second week.” Symptoms resolved. Note: symptoms occurred after dose increase.	Insufficient information. Concomitant meds not reported.
5092345 US	DC	Duloxetine dc. Positive dechallenge.	39 yo female prescribed duloxetine 30 mg QD for depression. Day 8, c/o urinary retention and extreme somnolence. PE neg for flank or suprapubic discomfort/fullness. Duloxetine dc. Day 16, UA WNL. Day 18, abdominal CT neg. Dx with elevated ALT/AST. Hx of ITP, liver failure, right heart failure. Events resolved.	Topiramate, bupropion, oxycodone – Topiramate and bupropion labeled for urinary retention; opiate agonists may cause urinary retention
4683134 US	DC	Symptoms resolving after dc Positive dechallenge	48 yo female with hx of urinary retention. Prescribed duloxetine 60 mg QD. After unknown time frame, c/o increased urinary retention and UTI. Also c/o musculoskeletal symptoms. Duloxetine dc. Symptoms resolving.	Hx of urinary retention, underlying UTI.
4599915 FOR	DC	Hx of incontinence Symptoms resolving after dc Positive dechallenge	43 yo female with hx of voiding difficulties, frequent UTIs and prior instrumentation of GU tract. Prescribed duloxetine 40 mg BID for stress incontinence. Within 1 st week, c/o urinary retention. Duloxetine dc. Recovering. Also c/o severe nausea, vomiting, fainting. Hx of MS.	Hx of voiding difficulties, frequent UTIs, prior instrumentation Insufficient information. Concomitant meds not reported.
4683065 US	DC	Symptoms resolved after dc Positive dechallenge	58 yo female prescribed duloxetine 30 QD for neuropathic pain after neck surgery. After unknown time frame, c/o “delay in urination.” Duloxetine dc. GU symptoms resolved. Also c/o GI, cardiac, CNS and ocular symptoms. GI, cardiac, and ocular symptoms resolved. CNS symptoms continued.	Morphine - opiate agonists may cause urinary retention; c/o concurrent CNS symptoms which continued after dc. No dx provided.
4877189 US	DC	Duloxetine dc. Positive dechallenge.	53 yo male with hx of urinary hesitation. Prescribed duloxetine 60 mg QD for OCD and depression. After 6-8 weeks, c/o increasing urinary hesitation. Also c/o musculoskeletal and lip pain. Duloxetine dc. Symptoms resolving.	Hx of urinary hesitation
4683130 US	DC	Duloxetine dc.	33 yo female prescribed duloxetine 60 mg. C/o hesitation, dysuria and UTI with E. coli, treated with cipro. UTI resolved with clear culture. Dysuria and hesitation continued. Duloxetine dc. Symptoms continued.	UTI; Symptoms continued after dc. Negative dechallenge. Insufficient information. Concomitant meds not reported.
5049634 US	DC	Duloxetine dc.	53 yo female prescribed duloxetine 30 mg QD for depression. Increased to 60 mg QD after 1 week. After dose increase, c/o urinary retention. Duloxetine dc. Symptoms continued. Note: date of duloxetine conflict – 2005 vs. 2006. Dose and duration information also conflicting in narrative vs. Section C.	atomoxetine labeled for urinary hesitation and retention. Negative dechallenge. Unclear information regarding concomitant.

ISR LOC	Medication Status/Medical intervention	Factors which increase strength of signal	Case Summary/Notes	Factors which decrease strength of signal
5044251 US	? DC – see note	Duloxetine dc.	Female of unknown age prescribed duloxetine 120 mg QD. C/O urinary retention. Duloxetine dc at unknown time. Symptoms resolved. Note: reporter unaware if duloxetine continued at time of retention.	Insufficient information. Concomitant meds not reported. Unclear information status of duloxetine at onset of retention.
4876839 US	DC	Duloxetine dc.	Male of unknown age with hx of urinary retention. Prescribed duloxetine 60 mg QD. C/O worsening of urinary retention and elevated PSA. Duloxetine dc.	Hx of urinary retention; Insufficient information. Concomitant meds and symptom resolution not reported.
4533504 US	DC	Duloxetine dc.	Female of unknown age prescribed duloxetine 30 mg QD. Within first week, c/o urinary hesitation. Duloxetine dc.	Insufficient information. Concomitant meds and symptom resolution not reported
4876467 US	DC	Duloxetine dc.	Male of unknown age prescribed duloxetine. C/O urinary hesitancy and STD. Treated with abx for STD. Duloxetine dc.	Underlying STD; Insufficient information. Concomitant meds and symptom resolution not reported.
4533185 US	DC	Duloxetine dc.	Male of unknown age prescribed duloxetine. C/O urinary hesitation. Duloxetine dc.	Insufficient information. Concomitant meds and symptom resolution not reported.
4533782 US	DC	Duloxetine dc.	Male in 50s prescribed duloxetine 60 mg QD for depression. On same day, c/o urinary retention. Duloxetine dc.	bupropion labeled for urinary retention. Insufficient information: symptom resolution not reported.
4651623 US	DC ER for ruptured ovarian cyst	Duloxetine dc.	18 yo female with hx of kidney stones. Prescribed duloxetine 30 mg QD for depression. Approximately 10 days later, c/o urinary retention. A few days after onset of urinary retention, seen in ER and dx with ruptured ovarian cyst. Duloxetine dc the same day.	Concurrent dx of ruptured ovarian cyst. Bupropion labeled for urinary retention. Anticholinergic effect of hyoscyamine sulfate may include urinary retention. Insufficient information: symptom resolution not reported.
4654426 US	DC	Duloxetine dc.	55 yo male prescribed duloxetine 30 mg QD for major depressive disorder. Increased to 30 mg BID after 10-14 days. During the second week, experienced multiple symptoms (GI, CNS, respiratory, musculoskeletal, neurologic, ocular, dermatologic) including urinary hesitation and retention. Duloxetine dc.	Topiramate labeled for urinary retention. Insufficient information: symptom resolution not reported.
4876603 US	DC	No concomitant meds. Duloxetine dc.	28 yo female prescribed duloxetine 30 mg QD for depression. No concomitant meds. 6.5 hours after first dose, c/o urinary retention. Multiple unrelated symptoms reported. Day 3, DC.	Insufficient information: symptom resolution not reported.
4531331 US	DC	Duloxetine dc.	Female of unknown age prescribed duloxetine 30 mg QD. C/O urinary hesitation within the first week. Duloxetine dc.	Insufficient information. Concomitant meds and symptom resolution not reported.
5050004 US	Continued	No concomitant meds. Symptoms continued.	46 yo female prescribed duloxetine 20 mg BID for depression. No concomitant meds. C/O hesitation.	Symptoms did not result in dc of duloxetine.
4531179 US	Continued	No concomitant meds. Symptoms continued.	45 yo female prescribed duloxetine 60 mg QD for major depressive disorder. No concomitant meds. C/O mild urinary hesitancy.	Symptoms did not result in dc of duloxetine.

ISR LOC	Medication Status/Medical intervention	Factors which increase strength of signal	Case Summary/Notes	Factors which decrease strength of signal
4531344 US	continued		55 yo female prescribed duloxetine 60 mg QD for depression. DC caffeine from diet. C/O urinary retention. Restarted caffeine in diet. Symptoms resolved.	Symptoms resolved while on duloxetine. Symptoms did not result in dc of duloxetine.
4531777 US	continued		36 yo female prescribed duloxetine 20 mg BID for depression. Same night, c/o urinary hesitation. Also c/o CNS and GI symptoms. Urinary hesitation resolved on Day 2.	Dicyclomine - antimuscarinic /antispasmodics may cause urinary hesitancy. Symptoms resolved while on duloxetine. Symptoms did not result in dc of duloxetine.
4683645 US	continued		58 yo female prescribed 60 mg QD for depression. C/O urinary hesitation with multiple bouts of being unable to void. Also nocturia. PE neg for distension. Hesitation gradually resolved over 3 weeks. UA neg.	Symptoms resolved while on duloxetine. Insufficient information. Concomitant meds not reported. Symptoms did not result in dc of duloxetine.
5044934 US	DC/Continued		27 yo female prescribed duloxetine 60 mg QD for major depression. C/O "difficulty urinating". Also c/o multiple GI and CNS symptoms.	Symptoms did not result in dc of duloxetine.
4533771 US	Continued		Male of unknown age prescribed duloxetine 30 mg QD for depression. Increased to 60 mg QD after 1 week. C/O urinary retention.	Bupropion labeled for urinary retention. Symptoms did not result in dc of duloxetine.
4877968 US	Continued		75 yo male prescribed duloxetine 20 mg QD for myoclonus. C/O urinary hesitancy.	Insufficient information: Concomitant meds not reported. Symptoms did not result in dc of duloxetine.
4682962 US	Continued		50 yo female prescribed duloxetine 60 mg QD. C/O urinary retention.	Insufficient information: Concomitant meds not reported. Symptoms did not result in dc of duloxetine.
4531366 US	Continued	no hx of prostate or urinary problems	68 yo male prescribed duloxetine 30 mg QD for peripheral neuropathy. Two days after first dose, c/o urinary hesitancy. Dose increased to 60 mg QD. Urinary hesitancy "improved slightly." Note: no hx of prostate or urinary problems	Insufficient information: Concomitant meds not reported. Symptoms did not result in dc of duloxetine.
4877974 US	Continued		77 yo male prescribed duloxetine 30 mg QD. After one week, increased to 60 mg QD. Prior to the dose increase, c/o urinary retention.	Insufficient information. Concomitant meds not reported. Symptoms did not result in dc of duloxetine.
4683635 US	Continued		57 yo female prescribed duloxetine 120 mg QD. C/O urinary retention. Chose to remain on duloxetine.	Fluphenazine labeled for urinary retention. Insufficient information: symptom resolution not reported. Symptoms did not result in dc of duloxetine.
4878063 4878055 US	Continued		45 yo male prescribed duloxetine 30 mg QD. Increased to 60 mg QD. After dose increase, co of urinary hesitancy. Decreased to 30 mg QD.	Insufficient information. Concomitant meds and symptom resolution not reported. Symptoms did not result in dc of duloxetine.
4531719 US	Continued		Female of unknown age prescribed duloxetine 30 mg QD. C/O urinary hesitation.	Insufficient information. Concomitant meds and symptom resolution not reported. Symptoms did not result in dc of duloxetine.
4613323 FOR	NR		31 yo female prescribed duloxetine 40 mg QD for urinary incontinence. Day 3, unable to void. Hx of spasticity by birth. Spasticity also increased in upper body to degree unable to care for self. Symptoms resolved.	Insufficient information: duloxetine status not reported.

ISR LOC	Medication Status/Medical intervention	Factors which increase strength of signal	Case Summary/Notes	Factors which decrease strength of signal
4876395 US	NR		64 yo female with hx of not being able to urinate with other antidepressants. Prescribed duloxetine 20 mg QD for depression. Within first few days, c/o trouble urinating with additional CNS, GI and ocular symptoms. Duloxetine continued for 11 days. Trouble urinating increased to not being able to urinate.	Hx of not being able to urinate with other antidepressants. Unclear information re: duloxetine status.
4929414 US	NR		Male of unknown age prescribed duloxetine and pregabalin. C/O urinary retention.	Insufficient information: duloxetine status and symptom resolution not reported.
4877183 US	NR		80 yo male with hx of frequent urination. Prescribed duloxetine “30-60 mg” QD for Parkinson’s disease. After 2 weeks, c/o difficulty urinating, increased nocturia. Duloxetine decreased to 30 mg QD.	trospium labeled for urinary retention. Insufficient information: duloxetine status and symptom resolution not reported.
4532937 US	NR		Female of unknown age prescribed duloxetine 30 mg QD. C/O urinary retention. Note: indicates no concomitant meds provided. Conflicts with statement “atomoxetine continued”.	atomoxetine labeled for urinary hesitation and retention. Insufficient information: duloxetine status and symptom resolution not reported.
4682991 US	NR		53 yo female prescribed duloxetine 30 mg QD for major depressive disorder. C/O urinary retention, blood in urine and “slight discomfort” during urination.	Fluoxetine and tiagabine labeled for urinary retention. Insufficient information: duloxetine status and symptom resolution not reported.
4531304 US	NR		80 yo male prescribed duloxetine 30 mg QD for depression. C/O urinary hesitation.	Insufficient information. Concomitant meds, duloxetine status and symptom resolution not reported.
4533132 US	NR		Male of unknown age prescribed duloxetine. C/O urinary retention.	Insufficient information. Concomitant meds, duloxetine status and symptom resolution not reported.
4531218 US	NR		Male of unknown age prescribed duloxetine. C/O “severe urinary hesitation.”	Insufficient information. Concomitant meds, duloxetine status and symptom resolution not reported.
4531216 US	NR		Male of unknown age prescribed duloxetine. C/O “severe urinary hesitation.”	Insufficient information. Concomitant meds, duloxetine status and symptom resolution not reported.

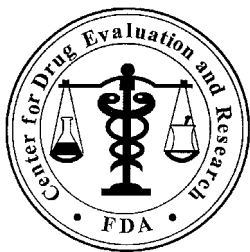
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/s/

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: August 6, 2008

To: Thomas Laughren, MD, Director, Division of Psychiatric Products (DPP)

Through: Mark Avigan, MD, Director, Division of Adverse Event Analysis 1
Solomon Iyasu MD, Director, Division of Epidemiology

From: Lois La Grenade, MD, MPH, Epidemiologist, Division of Epidemiology
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Laura Governale, Pharm.D., MBA, Drug Use Data Analysis Team Leader, Division of Epidemiology

Subject: Stevens-Johnson Syndrome (SJS) & Toxic epidermal Necrolysis (TEN)

Drug Name(s): SSRIs & SNRIs

Application Type/Number: See Table 1

Applicant/sponsor: See Table 1

OSE RCM #: 2007-2494

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.****

Table 1: Drugs Included in this Review & Approval Dates

Generic name	Trade name	NDA#	Approval date	Sponsor	Class
citalopram	Celexa	20-822	Jul 17, 1998	Forest	antidepressant
		21-046	Dec 22, 1999	Forest	antidepressant
	Citalopram	21-763	Dec 20, 2005	Biovail	antidepressant
duloxetine	Cymbalta	21-427	Aug 03, 2004	Lilly	antidepressant
		21-733	Sep 03, 2004		neuropathy pain
escitalopram	Lexapro	21-323	Aug 14, 2002	Forest	antidepressant
		21-365	Nov 27, 2002	Forest	antidepressant
	Escitalopram	21-440	Aug 29, 2002	Forest	antidepressant
fluoxetine	Prozac	18-936	Dec 29, 1987	Lilly	antidepressant
		20-101	Apr 24, 1991	Lilly	antidepressant
		20-187	Feb 28, 1994	Lilly	OCD
		20-974	Mar 09, 1999	Lilly	antidepressant
	Prozac weekly	21-235	Feb 26, 2001	Lilly	antidepressant
	Sarafem	21-860	May 19, 2006	Warner Chilcott	premenstrual
fluvoxamine	Luvox	20-243	Dec 30, 1991	Solvay	OCD
			Sep 3, 2003		withdrawn
paroxetine	Paxil	20-031	Dec 29, 1992	GlaxoSmithKline	antidepressant
	Paxil	20-710	Jun 25, 1997	GlaxoSmithKline	antidepressant
	Paxil	20-885	Oct 09, 1998	GlaxoSmithKline	antidepressant
	Paxil	20-936	Feb 16, 1999	GlaxoSmithKline	antidepressant
	Paxil CR	20-982	Feb 12, 2002	GlaxoSmithKline	panic
	Pexeva	21-299	Jul 03, 2003	JDS Pharms	OCD
sertraline	Zoloft	19-839	Dec 30, 1991	Pfizer	antidepressant
	Zoloft	20-990	Dec 7, 1999	Pfizer	OCD/panic
venlafaxine	Effexor	20-151	Dec 28, 1993	Wyeth	antidepressant
	Effexor XR	20-699	Oct 20, 1997	Wyeth	antidepressant

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EXECUTIVE SUMMARY

This consult is in response to a request from the Division of Psychiatric Products (DPP) to review cases and to compare reporting rates of serious skin disorders [Stevens - Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)] among the SSRIs and SNRIs.

The results indicated that for the first 41 months of marketing 4.7 million patients received prescriptions for duloxetine compared to 11 million for escitalopram. In the same time period the agency received reports of 13 cases of SJS/TEN with duloxetine and 4 cases with escitalopram. The reporting rate for duloxetine-associated SJS/TEN was approximately 2 – 4 times that of the background rate and approximately 7-fold greater than the reporting rate for escitalopram, which we consider the most valid comparator for the reporting rate analysis, since it was first marketed at a similar time. It was also higher than all the other SSRIs and SNRIs. The duloxetine case series included one death with a cause of death unrelated to the SJS, and one case without reported risk factors for SJS/TEN.

SJS/TEN has been associated with the SSRIs and the SNRIs, all of which include labeling for SJS/TEN in the postmarketing section. Although by definition SJS/TEN result in hospitalization and hospitalizations have been reported for all of the SSRI and SNRIs, duloxetine is the only SSRI/SNRI that includes postmarketing labeling for hospitalization with SJS/TEN.

Deaths were reported with SJS/TEN for duloxetine, fluoxetine, sertraline, and venlafaxine. The cases reported risk factors such as concomitant medications labeled for SJS/TEN or pre or comorbid conditions that may have contributed to the SJS/TEN; however, the SJS/TEN was reported as a contributing factor for cases with sertraline, venlafaxine, and fluoxetine therapy. Currently, sertraline is the only label that includes mention of possible fatalities with SJS/TEN.

OSE recommends the following:

- For duloxetine: We agree that the serious skin labeling should be elevated to the Warning and Precautions Section
- Make the Postmarketing labeling for all of the SNRIs and SNRIs consistent with the current duloxetine labeling language for hospitalizations and SJS/TEN
- Make the Postmarketing labeling for duloxetine, fluoxetine and venlafaxine consistent with the current sertraline labeling language for fatalities and SJS/TEN

1.1 INTRODUCTION

This consult is in response to a request from the Division of Psychiatric Products (DPP) to compare reported cases of serious skin disorders [Stevens - Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)] among the SSRIs and SNRIs. More specifically DPP is interested in how duloxetine reporting rates of SJS & TEN compare with rates of similar drugs in the class. The objective of this consult is therefore to review all domestic cases of SJS and TEN reported in the United States with SSRIs and SNRIs and to compare reporting rates of duloxetine to the other drugs.

1.2 REGULATORY HISTORY

Selective serotonin reuptake inhibitors (SSRIs) and selective serotonin-norepinephrine reuptake inhibitors (SNRIs) are oral antidepressant agents that are presumed to act by inhibiting CNS neuronal uptake of serotonin in the case of SSRIs and serotonin and norepinephrine in the case of SNRIs. Fluoxetine (Prozac®) was the first SSRI to be approved by the Agency, on December 29, 1987. The first SNRI to be approved was venlafaxine (Effexor®), approved on December 28, 1991. The complete list of these drugs is included in Table 1 on page 2 of this document.

An OSE consult on November 13, 2006¹ reviewed cases of SJS/TEN, including SJS, reported in association with duloxetine use. DPP was of the opinion that the eight cases of erythema multiforme (EM), SJS, and TEN constituted a strong enough signal to warrant a prominent position in the WARNINGS section of the label. But Lilly, duloxetine's sponsor, argued that it was no different from other SSRIs and SNRIs, all of which have serious skin disorders in the postmarketing Adverse Events sections of the labels. (See Appendix 7.1) To resolve the issue DPP has requested OSE to review domestic cases of SJS and TEN and compare reporting rates for duloxetine and the other SSRIs and SNRIs.

1.3 PRODUCT LABELING

The current duloxetine labeling includes a listing of SJS in the postmarketing section that has resulted in hospitalization. (See excerpt below.)

**Current Duloxetine Labeling
Postmarketing Spontaneous Reports²**

The following adverse reactions have been identified during postapproval use of Cymbalta. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Adverse reactions reported since market introduction that were temporally related to duloxetine therapy and not mentioned elsewhere

¹ Oluchi Elekwachi, DFS, November 13, 2006

² Cymbalta, NDA 21-427, approved on 11/28/07

in labeling include ...erythema multiforme... rash ...and urticaria. Serious skin reactions including Stevens-Johnson Syndrome that have required drug discontinuation and/or hospitalization have been reported with duloxetine.

Excerpts of the Postmarketing Adverse Events sections of the individual SSRI and SNRI labels are attached in Appendix 7.1. The SNRI and SSRI labels include a listing of serious skin reactions in the Postmarketing Adverse Events section, either SJS, TEN, epidermal necrolysis or a combination of the aforementioned. Duloxetine is the only SSRI or SNRI label that mentions hospitalization in association with serious skin reactions in the postmarketing labeling. In September of 1996, the DPP medical officer recommended adding postmarketing labeling for sertraline severe skin reactions with the language “occasionally fatal.”³ Fatalities associated with serious skin reactions are not labeled in the other SSRI or SNRI labels.

2 METHODS AND MATERIALS

2.1 AERS SEARCH

On March 18, 2008, safety reports were retrieved from the Agency’s Adverse Events Reporting System (AERS) database.

The AERS database was queried separately for the six SSRIs and the two SNRIs using the Standardized MedDRA Query (SMQ) for severe cutaneous adverse reactions (narrow). The narrow SMQ includes diagnosis terms that represent the three conditions - EM, SJS, and TEN.

See Appendix 7.2 for additional information regarding the SMQ for severe cutaneous adverse reactions (narrow).

See Appendix 7.3 for additional information regarding AERS.

2.2 CASE DEFINITION

OSE has developed working case definitions for postmarketing adverse drug reaction reviews. The standardized case definition for Stevens - Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) was used for this review. (See Appendix 7.4)

Inclusion Criteria

Adverse Event: All cases will be reviewed by a dermatologist to determine inclusion in the case series. As there has been confusion and changing nomenclature, the preferred MedDRA term (PT) Erythema Multiforme (EM) is included in the initial search strategy and all cases reporting a diagnosis of EM will be included in the initial case screening. All EM cases will be reviewed for histology results and the clinical description of extent

³ Mosholder, A. Medical Officer Review and Evaluation of Consultation, Subject: Sertraline and Serious Skin Adverse Drug Reactions, 09/23/1996.

of blisters and mucosal involvement to determine if the reported adverse event meets the current clinical description of an SJS/TEN event.

SJS/TEN Diagnostic Categories:

Cases with a **Probable** diagnosis of SJS/TEN must have resulted in hospitalization and have a documented diagnosis of SJS/TEN from a dermatologist. If SJS/TEN was not diagnosed by a dermatologist, the report should contain supportive evidence, (e.g., biopsy results) supporting the diagnosis.

Cases with a **Possible** diagnosis of SJS/TEN mention bullous conditions requiring hospitalization with a clinical description of extent of blisters and mucosal involvement. Cases in this category have not been confirmed by a dermatologist or did not provide biopsy results. This category includes consumer reports and reports listing SJS/TEN as part of the differential diagnosis at last report.

In addition, cases, which meet the clinical criteria for a SJS/TEN event, but did not result in hospitalization, will also be included in the case series.

Event does not meet case definition:

The following cases do not meet the case definition and should be excluded from further analysis: staphylococcal scalded skin syndrome (SSSS), linear IgA dermatosis, paraneoplastic pemphigus (PNP), acute graft-versus-host disease (AGVHD), drug-induced pemphigoid and pemphigus, acute generalized exanthematous pustulosis (AGEP), Toxic shock syndrome (TSS), and Kawasaki syndrome.

See Appendix 7.4 for additional information for the OSE case definition.

2.3 DRUG USE DATA

Drug Use Data Sources Used and Determining Settings of Care

Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

The IMS Health, IMS National Sales Perspectives™ (see APPENDIX 2 for full database descriptions and limitations) was used to determine the various retail and non-retail channels of distribution for fluoxetine, sertraline, paroxetine, venlafaxine, citalopram, escitalopram, duloxetine, and fluvoxamine.⁴ The examination of wholesale sales data for year 2007 indicates that at least 75% of bottles and packets of pills for these products were distributed to outpatient pharmacy settings. Outpatient pharmacy settings include chain, independent, food stores with pharmacies, and mail order pharmacies. For this review, we examined utilization patterns to assess outpatient population exposure not including mail order data.

⁴ IMS Health, IMS National Sales Perspectives™, Year 2007, Extracted 6-3-08. File: 0806venl.xls

We examined projected prescriptions for fluoxetine, sertraline, paroxetine, venlafaxine, citalopram, escitalopram, duloxetine, and fluvoxamine using Verispan, LLC: Vector One[®]: National (VONA) from initial marketing to December 2007, and projected number of patient filling a prescription for duloxetine and escitalopram using Verispan, LLC: Vector One[®]: Total Patient Tracker (TPT) for the first 41-months after initial marketing.

2.4 REPORTING RATE ANALYSIS TECHNIQUES

Steps in Chronological Order

US cases of SJS/TEN were retrieved and reviewed for duplicates and evidence of meeting the case definition and inclusion criteria. The numerator included all cases classified as a probable or possible diagnosis of SJS/TEN.

Three methods for calculating reporting rates were used. First we compared reporting rates for SJS/TEN with duloxetine and escitalopram in the first 3.4 years (411 months) of marketing. For this, we used cases derived from the AERS search as the numerator. To be included in the first 3.4 years, cases had to have an event date in the relevant time period. The received date was used if the event date was missing. The denominator was the estimated number of patients who received prescriptions for the two drugs in the respective time periods under review. The patient count method compares reporting rates between drugs, but not to the background rate.

We used a second method in order to be able to compare the reporting rate to the background rate (See footnote, Table 5). For this method the numerator was the same as in the first, but the denominator was total patient treatment years for each drug⁵. We restricted these methods to escitalopram as the only comparator because it was marketed closest in time to duloxetine and we consider this the most valid comparison, since secular trends may vary with different time periods.

The third method was used to compare duloxetine reporting rates to those for all other SSRIs and SNRIs currently on the market in the US (as requested by DPP). We used as the numerator all cases of SJS/TEN reported since initial marketing through December 31, 2007 that met the case definition and inclusion criteria. For the denominator we used projected total prescriptions dispensed from initial marketing through December 31, 2007. Prescriptions, rather than patient counts or total treatment time were used because OSE does not have access to patient level data prior to 2002 and many of the SSRIs were marketed initially much earlier than that. We therefore used the data that were available for that time period, namely, prescription level data. However there are inherent biases in comparing drugs with such different initial marketing times.

⁵ Data Source: Verispan, Vector One: National. Extracted Jun08. File: VONA 2007-2494 escitalopram total tx days 6-25-08.xls

3.1 AERS CASE SERIES

OSE retrieved reports from AERS and identified duplicates and cases that did not meet the case definition. (See Table 2.) Exclusions, due to the adverse event not meeting the serious skin case definition, were determined by a DAEA dermatologist.

Table 2. Exclusions

	Total Retrieved	Duplicates	Did not meet case definition	Final Case Series Total
citalopram	13	3	3	7
duloxetine	17	3	1	13
escitalopram	16	3	5	8
fluoxetine	39	5	19	15
fluvoxamine	10	1	7	2
paroxetine	45	2	28	15
sertraline	96	8	65	23
venlafaxine	39	3	22	14

The case series and are characterized in Table 3 below.

Table 3. Demographics and Clinical Characteristics for Unique US SJS/TEN SSRI and SNRI AERS Cases with an Event Date or an FDA received Date from Initial Marketing through December 2007

Selected Characteristics*	Duloxetine n = 13	Escitalopram n = 8	Fluoxetine n = 15	Fluvoxamine n = 2	Paroxetine n = 15	Sertraline n = 23	Venlafaxine n = 14	Citalopram n = 7
Approval Date	8/3/2004	8/14/2002	12/29/1987	12/30/1991	12/29/1992	12/30/1991	12/28/1993	7/17/1998
Age (years)								
Range	20 - 80	15 - 60	11 - 73	20 - 76	23 - 63	14 - 88	20 - 71	28 - 84
Median	55	42	31	49	44	37	52	52
Mean	52	40	34	49	43	44	50	60
Gender								
Female	11	7	4	2	10	11	10	4
Male	1	1	11	0	2	9	3	3
Time to onset (days)								
Range	0.5 - 42	9 - 83	2 - 236	15 - 548	3 - 1095	2 - 180	6 - 90	3 - 90
Median	8	21	16	277	38	25	26	13
Mean	18	33	42	277	232	63	41	24
Peak Daily dose (mg)								
Range	20 - 60	5 - 20	10 - 75	50 - 100	10 - 60	20 - 100	50 - 300	10 - 20
Median	60	10	20	75	20	50	263	20
Mean	53	15	27	75	27	65	169	17
Outcome								
Hospitalized	3	6	8	1	7	13	6	3
Death	1	0	4	0	0	2	2	0

*Not all cases had data on every characteristic listed in Table. See Appendix 7.5 for additional information.

The duloxetine case series included one death (AERS ISR #4860668); however, the 80 year old female patient with a history of congestive heart failure, ischemic colitis, severe degenerative arthritis, and mild renal failure was noted to have fully recovered from the SJS during the hospitalization. The reported cause of death was congestive heart failure.

Deaths were also reported for two of the SSRIs, sertraline and fluoxetine, and the remaining SNRI, venlafaxine. The cause of death (AERS ISR #1436700) was reported as a perforating duodenal ulcer in a patient 72 year old male patient who developed severe EM after coronary artery bypass graft surgery, while taking sertraline. The coroner noted the severe bullous EM was probably an allergic reaction to sertraline and listed significant conditions contributing to the patient's death as hypertension, atherosclerotic cardiovascular disease, and severe bullous EM. The second sertraline case (AERS ISR #3001088) did not identify a cause of death, reporting that the patient developed a rare skin disease, possibly SJS, TEN, or EM, and died while on sertraline and an unidentified diuretic. The venlafaxine death (AER ISR #4677929) was reported by the spouse who noted the official cause of death was spontaneous subarachnoid hemorrhage with other significant conditions contributing to the death listed as sepsis and TEN. Per the report, the patient developed the complications after a reportedly successful brain surgery.

Four deaths were reported with fluoxetine. One death (AERS ISR #5095476) reported concomitant medications labeled for SJS that were started at the same time as fluoxetine. AERS ISR #4677929, previously summarized above, is included in the fluoxetine deaths. The cause of death for AERS ISR #3822384 was reported as staph aureus septic shock with renal involvement leading to respiratory insufficiency, rhabdomyolysis, disseminated intravascular coagulation, complicated by TEN (drug reaction, probably nafcillin). Staph Aureus was identified in both knees and one elbow and the patient was diagnosed with osteomyelitis. AERS ISR #517812 describes the case of a 27 year old male with AIDS who developed fulminant hepatic failure, acute tubular necrosis, GI bleeding and "bleeding from all sites", followed by development of a desquamating rash. The cause of death was not reported.

Table 4 shows a comparison of hospitalized serious skin cases for all the drugs. Hospitalizations for SJS/TEN reactions were reported for citalopram (1), fluoxetine therapy (3), paroxetine (2), and sertraline (1) that did not report additional risk factors such as concomitant medications labeled for SJS/TEN or pre or comorbid medical conditions that may have contributed to the SJS/TEN.

Table 4: AERS SSRI and SNRI US SJS/TEN Cases Received by the FDA from Marketing through March 18, 2008 with a Reported Hospitalization

Drug	Approval Date	#Hospitalizations/ #SJS/TEN Cases	# Hospitalizations/Cases <u>without Reported Risk</u> Factors for SJS/TEN
citalopram	08/17/1998	3/7	1/3
duloxetine	08/3/2004	3/13	0/1
escitalopram	08/14/2002	6/8	none
fluoxetine	12/29/1987	8/15	3/3
fluvoxamine	12/5/1994	1/2	none
paroxetine	12/29/1992	7/18	2/2
sertraline	12/30/1991	13/23	1/2
venlafaxine	12/28/1993	6/14	none

One duloxetine case without risk factors such as concomitant medications or pre or comorbid medical conditions that may have contributed to the SJS/TEN was identified. The case is summarized below:

AERS ISR #556590

A physician reported the case of a 20 year old female who was not taking any concomitant medications. She started duloxetine 30mg daily for the treatment of a generalized anxiety disorder. After 14 days, the dose was increased to 60mg. One week after the dose increase, the patient experienced a fever, exfoliation on her palms and the bottoms of her feet, blistering on her hands, lesions in her oral mucosa and a truncal rash. The physician discontinued the duloxetine and referred the patient to a dermatologist who saw her the same day. The dermatologist diagnosed SJS and prescribed oral prednisone. The patient was not hospitalized. One week later, the physician examined the patient and noted her symptoms had improved. The event resolved. The physician felt the event was related to duloxetine.

Cases without risk factors such as concomitant medications and/or pre or comorbid medical conditions that may have contributed to the SJS/TEN were also identified for citalopram (3), fluoxetine (3), sertraline (2), and paroxetine (2). In addition, a positive rechallenge case with fluoxetine is summarized below.

AERS ISR #542949

A physician reported the case of a 23 year old male prescribed fluoxetine 40mg daily for depression and anxiety. After approximately four weeks of fluoxetine therapy, over a two day period, the patient developed target lesions on the extremities and face with arthralgia and myalgia. Fluoxetine was discontinued and a decrease in symptoms was noted. Fluoxetine was restarted and the patient developed dyspnea, periorbital edema, arthralgias, and new skin lesions. The patient was diagnosed with EM. A rheumatologist was consulted and confirmed the diagnosis. The patient's medical history was negative for risk factors and the patient was not taking concomitant medication. A history of aspirin allergy was reported.

3.2 REPORTING RATES AND DRUG USE

Table 5. Projected Total Patient Counts, Therapy Years & Reporting Rates for SJS/TEN in first 41 months of marketing

Drug	Projected Patient Counts	Total US SJS/TEN Cases	Reporting Rates/10 ⁶ patients Treated	Total Therapy Years***	Reporting Rates/10 ⁶ person years	Background Rate [±]
Duloxetine*	4,696,386	13	2.8	2,194,895	5.9	1-2/10 ⁶ /year
Escitalopram**	11,116,889	4	0.4	5,209,103	0.8	

*Source: Verispan, Vector One: Total Patient Tracker. August 2004 – December 2007. Extracted Jan08

File: TPT 2007-2494 Lex Cym 1-16-08 Y02-07 Aggregate.xls

**Source: Verispan, Vector One: Total Patient Tracker. August 2002 – December 2005. Extracted Mar08.

File: TPT 2007-2494 Lexapro Aggregate Aug02-Dec05 3-7-08.xls

*** Source: Verispan, Vector One: National. Extracted Jun08. File: VONA 2007-2494 escitalopram total tx days 6-25-08.xls

± Mockenhaupt M, Schopf E. Epidemiology of drug-induced severe skin reactions. Semin Cutan Med Surg. 1996 Dec;15(4):236-43.

Table 6. Total Retail Prescriptions* & SJS/TEN Reporting Rates (Per million Prescriptions) for SSRIs & SNRIs from initial marketing to December 2007

Drug	Total Prescriptions	SJS/TEN Cases	Reporting Rates/10 ⁸ Rxs
Duloxetine HCl	26,567,509	13	48.9
Fluvoxamine maleate	13,405,295	2	14.9
Venlafaxine HCl	152,855,579	14	9.2
Sertraline hydrochloride	322,554,463	23	7.1
Escitalopram/oxalate	114,983,548	8	7.0
Paroxetine	266,007,704	15	5.6
Citalopram hydrobromide	117,490,238	6	5.1
Fluoxetine	345,606,763	15	4.3

*Source: Verispan, Vector One: National. Years 1991 - 2007. Extracted 2-4-08. File: VONA 2007-2494 TRx 91-07 SSRI SNRI 2-4-08.xls

4

DISCUSSION

The results indicate that reporting rates for SJS/TEN are higher with duloxetine use than with the other SSRIs & SNRIs. Compared to escitalopram, which was marketed at approximately a similar time to duloxetine, the rate for duloxetine was approximately 7 times that for escitalopram and 3 – 6 times the background rate in the first 41 months of marketing. This reporting rate ratio of 7 for duloxetine compared to escitalopram was remarkably consistent for all three methods used: the patient count method, and the person-time method for the first 41 months of marketing, as well as the total prescriptions method. We confined the traditional person-time reporting rate calculation to only escitalopram as comparator because all the other drugs in the class were approved much earlier than duloxetine. It is well known that factors that affect reporting of adverse events include secular trends, so that valid comparisons should only be made between drugs marketed at similar times.

However, since we were requested to compare reporting rates for all the SSRIs & SNRIs we attempted to place all cases reported in the context of drug use. These results are reflected in Table 6 and reported as cases per 10⁸ prescriptions dispensed. The reporting

rate for SJS/TEN with duloxetine was the highest of all the comparators and remained roughly 7 times that of escitalopram. The rate for duloxetine was also more than 3 times that of the second highest reporting rate, duloxetine 48.9 vs. fluvoxamine 14.9 per 10 million prescriptions.

SJS/TEN has been associated with the SSRIs and the SNRIs, all of which include label for SJS/TEN in the postmarketing section. Although by definition SJS/TEN result in hospitalization and hospitalizations have been reported for all of the SSRI and SNRIs, duloxetine is the only SSRI/SNRI that includes postmarketing labeling for hospitalization with SJS/TEN.

Deaths were reported with SJS/TEN for duloxetine, fluoxetine, sertraline, and venlafaxine. The cases reported risk factors such as concomitant medications labeled for SJS/TEN or pre or comorbid conditions that may have contributed to the SJS/TEN; however, the SJS/TEN was reported as a contributing factor for cases with sertraline, venlafaxine, and fluoxetine therapy. Currently, sertraline is the only label that includes mention of possible fatalities with SJS/TEN.

5 CONCLUSION

We conclude that duloxetine use appears to be associated with an increased risk of SJS/TEN based on reporting rate calculations. We agree that labeling needs to be strengthened with more prominent positioning of this adverse event in the duloxetine label, in the WARNINGS & PRECAUTIONS section.

The postmarketing labeling regarding hospitalizations and fatalities for the SSRIs and the SNRIs appears inconsistent with the reported outcomes in the cases received by the FDA. The current labeling for the SSRIs and venlafaxine does not sufficiently represent the potential for a serious adverse skin reaction to require hospitalization. The current labeling for the SNRIs and the SSRIs is inconsistent regarding the potential for fatalities with SJS/TEN.

6 RECOMMENDATIONS

OSE therefore recommends the following:

- For duloxetine: We agree that the serious skin labeling should be elevated to the Warning and Precautions Section
- Standardize the Postmarketing labeling for all of the SNRIs and SNRIs consistent with the current duloxetine labeling language for hospitalizations and SJS/TEN
- Standardize the Postmarketing labeling for duloxetine, fluoxetine and venlafaxine consistent with the current sertraline labeling language for fatalities and SJS/TEN

7.1 RELEVANT TRUNCATED EXCERPTS FROM SSRI & SNRI LABELS

(Source: PDR® Electronic Library™, accessed February 14, 2008, except fluvoxamine, source: label approved 12/20/07, Drugs@FDA)

Citalopram (Celexa)

Other Events Observed During the Postmarketing Evaluation of Celexa (citalopram HBr)

It is estimated that over 30 million patients have been treated with Celexa since market introduction. Although no causal relationship to Celexa treatment has been found, the following adverse events have been reported to be temporally associated with Celexa treatment, and have not been described elsewhere in labeling: **toxic epidermal necrolysis, epidermal necrolysis, erythema multiforme,**

Escitaloprim (Lexapro)

Events Reported Subsequent to the Marketing of Escitalopram

Although no causal relationship to escitalopram treatment has been found, the following adverse events have been reported to have occurred in patients and to be temporally associated with escitalopram treatment during post marketing experience and were not observed during the premarketing evaluation of escitalopram: erythema multiforme, photosensitivity reaction, **Stevens Johnson Syndrome, toxic epidermal necrolysis,**

Fluoxetine (Prozac)

Postintroduction Reports

Voluntary reports of adverse events temporally associated with Prozac that have been received since market introduction and that may have no causal relationship with the drug include the following: epidermal necrolysis, erythema multiforme, erythema nodosum, exfoliative dermatitis, **Stevens-Johnson syndrome,**

Fluvoxamine (Luvox)

Postmarketing Reports

Voluntary reports of adverse events in patients taking LUVOX Tablets that have been received since market introduction and are of unknown causal relationship to LUVOX Tablets use include: bullous eruption, Henoch-Schoenlein purpura, **Stevens-Johnson syndrome, toxic epidermal necrolysis,**

Paxil (Paroxetine)

Postmarketing Reports: Voluntary reports of adverse events in patients taking PAXIL that have been received since market introduction and not listed above that may have no causal relationship with the drug include ...toxic epidermal necrolysis,

Venlafaxine (Effexor)

Postmarketing Reports

Voluntary reports of other adverse events temporally associated with the use of venlafaxine that have been received since market introduction and that may have no causal relationship with the use of venlafaxine include the following: **epidermal necrosis/Stevens-Johnson Syndrome, erythema multiforme,**

Zoloft (Sertraline)

Other Events Observed During the Postmarketing Evaluation of ZOLOFT—Reports of adverse events temporally associated with ZOLOFT that have been received since market introduction, that are not listed above and that may have no causal relationship with the drug, include the following: **severe skin reactions, which potentially can be fatal, such as Stevens-Johnson syndrome, vasculitis, photosensitivity and other severe cutaneous disorders,**

7.2 STANDARDIZED MEDDRA QUERY

(Source SMQ Introductory Guide V10.1, September 2007, MSSO-DI-6226-10.1.0)

2.50 Severe cutaneous adverse reactions (SMQ)

(Production Release April 2005)

2.50.1 Definition

This SMQ was developed to identify cases of severe, sometimes life-threatening skin reactions that are often drug-induced.

Severe cutaneous adverse reactions (SCARs) include

- Erythema multiforme

EM is an acute disease characterized by symmetrically distributed papular lesions affecting mainly the extremities, often with mucosal erosions. The typical lesion is target-shaped; it is concentrically organized with three different colored zones, often with a blister in the center, and it is clearly demarcated from the surrounding skin. There may be general symptoms such as fever and malaise.

- Stevens-Johnson syndrome

SJS is characterized by widespread skin lesions which may either be target shaped or consist of erythematous macules with epidermal detachment, together with severe mucosal erosions. SJS includes erosions of the skin up to 10% of body surface area. The general symptoms are more marked than in erythema multiforme.

- Toxic epidermal necrolysis

TEN is characterized by widespread erythematous areas with epithelial necrosis and epidermal detachment exceeding 10% body surface area, leaving bare dermis. There are often also small erythematous or purpuric lesions with or without blisters. Extensive mucosal erosions are frequent. General symptoms, usually severe, include high fever, malaise, and painful skin. According to CIOMS

definitions, these conditions are characterised by blisters (bullous reactions); they have traditionally been regarded as related disorders, with occasionally overlapping signs and symptoms. Similar disorders include necrosis of keratinocytes, leading to blisters and epidermal detachment.

Individual SMQs

2.50.2 Inclusion/Exclusion Criteria

Narrow scope: diagnosis terms that represent the three conditions (EM, SJS, TEN) are included.

- Broad scope: MedDRA PTs that represent the signs/symptoms included in the criteria for the diagnoses of each of the three conditions (EM, SJS, TEN) are included.
- MedDRA PTs that are signs or symptoms of a skin condition but not included in the criteria for the diagnosis of EM, SJS, and TEN are excluded, e.g., PT *Dermatitis herpetiformis* and PT *Keratolysis exfoliativa acquired*.
- General, non-specific, and often mild skin reactions (e.g., rash) are excluded, e.g., PT *Ulcer* and PT *Vascular skin disorder*.

2.50.3 List of References for Severe cutaneous adverse reactions (SMQ)

- Roujeau JC and Stern RS. Severe adverse cutaneous reactions to drugs. *New England Journal of Medicine* 1994; 331: 1272-1285.
- Reporting Adverse Drug Reactions. Definitions of terms and criteria for their use. *CIOMS publication*, Geneva 1999.

7.3 LIMITATIONS OF AERS

The voluntary or spontaneous reporting of adverse events from health care professionals and consumers in the U.S reflects underreporting and also duplicate reporting. For any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s). The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues. Therefore, counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing drug risk between drugs.

7.4 CASE DEFINITION: STEVENS JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) DISEASE/ADVERSE EVENT(S)

Definition

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are rare, potentially life-threatening acute reactions of the skin characterized by keratinocyte apoptosis resulting in erosions of the mucous membranes, separation of the epidermis from the dermis, and severe constitutional symptoms.^{6,7}

Etiology

SJS was described by Stevens and Johnson in 1922 as “an extraordinary, generalized eruption with continued fever, inflamed buccal mucosa and severe purulent conjunctivitis” in 2 patients. In 1956 Lyell described 4 patients with an acute rash followed by skin detachment and mucous membrane involvement and proposed the name TEN. He described the eruption as “resembling scalding of the skin objectively and subjectively.” Lyell also postulated that a circulating toxin caused the damage to the epidermis.⁸

Over the intervening years, it was postulated that erythema multiforme (EM) major, SJS and TEN were variants of the same bullous erythema multiforme spectrum. In 1993, consensus definitions were developed for EM major, SJS and TEN and EM was classified as a different disease than SJS and TEN.^{3, 9, 10} In the past, EM was used to describe patients now designated as having SJS. EM is now used by most to describe patients with typical “target” lesions appearing on limbs and appendages as a result of an infection, most commonly herpes simplex virus. EM major has a mild clinical course with limited mucosal involvement (usually only the oral mucosa) and frequent recurrences.⁵ EM is thus a different disease than SJS and TEN, but is mentioned herein for consideration when reviewing older reports or reports from non-specialists that may be inaccurately coded in the AERS database.

The pathogenesis of SJS and TEN is poorly understood and may be partly an immunologic and partly a genetic predisposition. The tendency to develop SJS or TEN may be due to an impaired capacity to detoxify reactive intermediate drug metabolites. It is thought to be initiated by an immune response to an antigenic complex formed by the reaction of such metabolites with certain host tissues. Genetic susceptibility may also play a role.^{1, 11}

⁶ French LE. Toxic Epidermal Necrolysis and Stevens Johnson syndrome: our current understanding. *Allergology International* 2006; 55(1):9-16.

⁷ Dermatology ed. Bologna 2004, Chapters 21 & 22.

⁸ Letko E, Papaliodis DN, Papaliodis GN, Daoud YJ, Ahmed AR, Foster CS. Stevens-Johnson syndrome and toxic epidermal necrolysis: a review of the literature. *Ann Allergy Asthma Immunol.* 2005 Apr;94(4):419-436.

⁹ Mockenhaupt M, Schopf. Epidemiology of Drug-Induced Severe Skin Reactions. *Seminars in Cutaneous Medicine and Surgery.* 1996;15(4):236-243)

¹⁰ Pereira FA, Mudgil AV, Rosmarin DM. Toxic epidermal necrolysis. *J Am Acad Dermatol* 2007 Feb;56(2):181-200.

¹¹ Brady WJ, Perron AD, DeBehnke DJ. Chapter 246. Serious Generalized Skin Disorders. In: *Emergency Medicine: A Comprehensive Study Guide*, 6th edition (2004).

The hallmark of SJS and TEN is epidermal necrosis due to apoptosis of keratinocytes. Apoptosis is mediated by cytokine release from activated CD8 cytotoxic T-cells, which leads to necrosis and sloughing of the epidermis. Currently there is much interest in the soluble Fas ligand, interferon gamma, tumor necrosis factor (TNF)-alpha, nitric oxide synthase and other cytokines and their role in the development of SJS and TEN.⁵

Classification

Differentiation among cases of SJS and TEN depends on the nature of the skin lesions and extent of body surface area involvement. The more severe forms of TEN have a greater percentage of body surface area of epidermal detachment. Target lesions tend to change from the classic, raised, three-ringed iris lesion to a more purpuric or erythematous two ringed lesion. Clinically, each of these reaction patterns is characterized by the presence of the triad of mucous membrane erosions, target lesions, and epidermal necrosis with skin detachment. Some SJS cases are not drug related and may develop after other predisposing factors, including infections (e.g., mycoplasma-induced pneumonia), neoplasm, autoimmune diseases, and immunizations.^{1,12}

Table 1. Current Classification of SJS and TEN^{4,5,6}

Type	% of body surface area involvement	Description of lesions
SJS	< 10% epidermal detachment	Widespread erythematous or purpuric macules or flat atypical targets
SJS/TEN overlap	10- 30% epidermal detachment	Widespread purpuric macules or flat atypical targets
TEN	> 30% epidermal detachment	Widespread purpuric macules or flat atypical targets ("spots" may or may not be present)

Epidemiology

SJS and TEN are extremely rare bullous skin reactions that are almost exclusively associated with medications. The incidence rate for SJS and TEN in industrialized countries is 1-2 cases per million population.¹³ In Europe, the incidence of both SJS and TEN is approximately 2 patients per million people per year based on a prospective registry of hospitalized patients.⁴ The incidence of TEN is generally higher in HIV-infected patients, particularly those with advanced disease.⁵ For instance, the incidence of TEN in adults secondary to sulfamethoxazole-trimethoprim was 2.6 cases per 100,000 exposures, but this number increases to 8.4 cases per 100,000 exposures in HIV-positive patients.⁷

Patients particularly at risk for SJS or TEN are slow acetylators and immunocompromised patients (i.e. HIV infection, lymphoma).¹ Other risk factors for SJS or TEN include radiotherapy for brain tumors (particularly with phenytoin) or Asian heritage (particularly for carbamazepine, phenytoin and allopurinol). If a first-degree relative has a history of a serious skin reaction to a particular medication, the patient is also at risk.⁵

SJS occurs predominantly in children and adolescents,^{1,5} while TEN occurs in patients of any age.^{4,5,6} The primary complications of SJS and TEN are infection and hypovolemia with electrolyte disorders. SJS has a mortality rate of approximately 5%.^{1,7} TEN has a mortality rate of approximately 30%.^{4,5,6} In cases of SJS/TEN overlap, the mortality rate is between 5-30%.⁵

Drug-induced SJS or TEN has been described in the literature for more than 200 medications (see Table 2 below for more commonly associated medications). Medications are believed to cause SJS or TEN through haptens, prohaptens (reactive metabolites) and direct reactions. The majority of drugs are prohaptens; the chemically inert parent drug does not itself act as a hapten, but a chemically reactive intermediate is formed during metabolism. The period of greatest risk for developing SJS or TEN is in the first two months of treatment. Patients with slow acetylators and patients with brain tumors who are undergoing radiotherapy and concomitantly receiving phenytoin are particularly at risk for SJS and TEN.^{1,5}

Table 2. Classes of Medications Commonly Reported in the Literature to be Associated with SJS or TEN*^{5,8,14,15,16}

Pharmacologic or Therapeutic Class	Common Example	Comment
Sulfonamides (particularly antibacterials)	Trimethoprim/sulfamethoxazole	Related to arylamine group at N4 position and highly reactive metabolite
Aromatic Anticonvulsants	Phenobarbital Carbamazepine Phenytoin	Cross-reactivity between the 3 products.
Beta-lactam antibiotics	Penicillin Cephalosporins	Potentially confounded by indication
Non-steroidal anti-inflammatories (particularly oxicams)	Piroxicam Meloxicam Sulfasalazine	
COX-2 Inhibitors	Valdecoxib (withdrawn)	Valdecoxib & celecoxib have

¹² Knowles SR, Shear NH. Recognition and management of severe cutaneous drug reactions. *Dermatol Clin* 2007;25:245-253.

¹³ La Grenade L, Lee J, Weaver J, Bonnel R, Karwoski C, Governale L, Brinker A. Comparison of Reporting of Stevens-Johnson syndrome and Toxic Epidermal Necrolysis in Association with Selective COX-2 Inhibitors. *Drug Safety* 2005;28(10):917-924.

¹⁴ Roujeau J-C Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *NEJM* 1995;333:1600-1607.

¹⁵ Mockenhaupt M, Viboud C, Dunant A, et al. Stevens-Johnson syndrome and Toxic Epidermal Necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-Study. *Journal of Investigative Dermatology*. 2008;128(1):35-44.

¹⁶ Chosidow OM, Stern RS, Wintroub BU. Chapter 50. Cutaneous drug reactions. In: *Harrison's Principles of Internal Medicine*, 16th Ed. (2005).

(particularly with sulfonamide group)	Celecoxib Rofecoxib (withdrawn)	sulfonamide groups
HIV treatments	Nevirapine Abacavir Dapsone	
Xanthine Oxidase Inhibitors	Allopurinol	
Tuberculosis treatments	Rifampin Isoniazid Thiacetazone	
Miscellaneous Antibiotics	Tetracyclines Quinolones	Potentially confounded by indication
Miscellaneous Anticonvulsants	Lamotrigine Valproic Acid	Valproic acid potentially confounded by concomitant medication, questionable based on EuroSCAR-study.
Antifungals (particularly imidazoles)	Fluconazole Ketoconazole Miconazole	Potentially confounded by indication
Antidepressants	Sertraline	

* List is not all-inclusive.

Clinical Manifestations

Presentation

Initial symptoms of both SJS and TEN can be fever, stinging eyes, and pain upon swallowing, which can precede skin lesions by 1-3 days. Skin lesions appear first on the trunk, spreading to the neck, face and proximal upper extremities. The distal portions of the arms as well as the legs are relatively spared, but the palms and soles can be an early site of involvement. Erythema and erosions of the buccal, ocular and genital mucosa are present in more than 90% of patients. The respiratory epithelium is involved in 25% of TEN cases and gastrointestinal lesions can also occur. The skin lesions are usually tender and mucosal erosions are very painful. The skin lesions are initially erythematous, dusky-red, or purpuric macules of irregular size and shape and tend to coalesce. As the epidermal involvement progresses to full-thickness necrosis, the dusky-red macular lesions begin to look gray. The necrotic epidermis detaches from the underlying dermis and fluid fills the space between the dermis and epidermis, producing blisters. The blisters break easily and can be extended sideways by slight pressure of the thumb (Nikolsky sign). The skin easily pulls away, revealing large area of raw and bleeding dermis.¹

Diagnosis

Histology

Histological examination of skin lesions shows epidermal necrosis (pathognomonic finding). Early lesions show scattered necrotic keratinocytes in the epidermis. Late stage lesions show confluent “full-thickness” epidermal necrosis, which eventually forms subepidermal bullae.⁵

Differential Diagnosis:

Staphylococcal scalded skin syndrome (SSSS), linear IgA dermatosis, paraneoplastic pemphigus (PNP), acute graft-versus-host disease (AGVHD), drug-induced pemphigoid and pemphigus, acute generalized exanthematous pustulosis (AGEP), Toxic shock syndrome (TSS), and Kawasaki syndrome.

Treatment

The suspect medication(s) should be discontinued as soon as possible and the patient should receive supportive care in a burn unit due to fluid and electrolyte loss and the risk of infection. These patients are at risk for sepsis, multiorgan failure, pulmonary embolism and gastrointestinal hemorrhage. The mucosal involvement may also lead to poor intake and absorption from the gastrointestinal tract and tracheobronchial mucosal sloughing. Skin sequelae include vaginal, urethral and anal strictures; loss of nails; scarring; and pigmentation abnormalities. The ocular involvement may also lead to visual disorders, including blindness.⁵

Various treatments affecting immune responses or cytokines are being studied, but the trials are not well-controlled due to the rarity of the event. Treatments that have been studied include intravenous immunoglobulin (IVIG), systemic steroids, plasmapheresis, cyclosporine, cyclophosphamide and anti-TNF therapies.

AERS search strategy (MedDRA version 10.1)

A Standardized MedDRA Query (SMQ) for Severe Cutaneous Adverse Reactions is available, including:

- Narrow search: Specific search terms for severe cutaneous adverse reactions (SMQ) – see OSE website for specific terms.
- Broad search: includes the search terms for severe cutaneous adverse reactions (SMQ) narrow plus more general search terms (e.g. blister, drug eruption, skin erosion) – see OSE website for specific terms.

OSE Case Definition of SJS or TEN

Inclusion Criteria

All cases are categorized as probable or possible events of SJS or TEN. Since there has been confusion and changing nomenclature, EM should be included in the initial search strategy and initial case screening. The reports of EM should be reviewed for histology

results and the clinical description of extent of blisters and mucosal involvement to determine if these are reports of SJS or TEN. A dermatologist may be consulted for reports that are difficult to categorize.

Probable cases must have a documented diagnosis of SJS or TEN from a dermatologist. If SJS or TEN was not diagnosed by a dermatologist, the report should contain supportive evidence, (e.g., biopsy results) supporting the diagnosis and state that the patient was hospitalized for the condition.

Possible cases mention bullous conditions requiring hospitalization with clinical description of extent of blisters and mucosal involvement. Cases in this category have not been confirmed by a dermatologist or do not provide biopsy results. This category includes consumer reports and reports listing SJS or TEN as part of the differential diagnosis at last report.

Event does not meet case definition:

The following cases do not meet the case definition and should be excluded from further analysis: staphylococcal scalded skin syndrome (SSSS), linear IgA dermatosis, paraneoplastic pemphigus (PNP), acute graft-versus-host disease (AGVHD), drug-induced pemphigoid and pemphigus, acute generalized exanthematous pustulosis (AGEP), Toxic shock syndrome (TSS), and Kawasaki syndrome.

7.5 CASE SERIES TABLE

ISNRUM	SEX	AGE/ YEARS	TIME TO ONSET	PEAK DAILY DOSE/ MG	OUTC 1	OUTC 2	OUTC 3	OUTC 4	OUTC 5
CITALOPRAM									
3668447	Male	45	42 days	20	OT				
3827535	Male	U	nr	nr	OT				
3938447	Female	76	?2 weeks	20	HO				
4193106	Female	78	10 days to rash 11 days to dx	10	OT	RI			
4561233	Male	45	? 3 months	20	HO				
4616396	Female	48	12 days to rash, 15 days to dx	20	OT				
4809458	Female	84	3 days	10	OT				
DULOXETINE									
4475362	Female	81	3 days	60	OT				
4509726	Female	U	?6-7weeks	nr	OT				
4563802	Female	60	?9 days, 1-2 days after dose increase	60	OT				
4579444	Female	U	nr	nr	HO				
4614274	Female	U	? A few weeks	60	HO	OT			
4860668	Female	80	10-12 hours	60	DE	HO	OT		
4928808	Female	55	? 7 days	nr	LT	HO	OT		
5023018	Unk	U	3 days	20	OT				
5036025	Female	42	? 4 weeks	60	HO				
5102511	Female	56	? Days	60	LT	OT			
5225559	Male	55	3 days	30	OT				
5340486	Female	47	?35 days	60	OT				
5569590	Female	20	3 weeks, 1 week after dose increase	60	OT				
ESCITALOPRAM									
4095207	Female	15	?32 days	nr	HO				
4424990	Female	57	9 days	10	HO	RI			
4542148	Female	55	20	20	OT				
4983662	Female	20	? 3 weeks	5	HO				
5007264	Female	42	83 days	nr	HO				
5081343	Female	60	nr	nr	HO				
5419390	Male	41	nr	nr	LT	HO			
5468555	Female	29	nr	10	HO	OT			
FLUOXETINE									

517812	Male	27	? 10 days	nr	DE	HO			
542949	Male	23	34 days	40	HO				
632743	Male	31	5 days	20	HO				
671043	Female	18	3 weeks	20	HO				
708836	Male	30	5 days	20	HO				
722264	Male	25	nr	nr	HO				
797009	Female	36	nr	20	HO				
1449386	Female	36	3 weeks	20	HO				
1510574	Male	37	nr	20	HO				
3216028	Female	33	2 days	nr	OT				
3822384	Male	60	78 days	75	DE	LT	HO		
4677929	Male	54	nr	nr	DE				
4838933	Male	11	236 days	10	LT				
5095476	Male	73	nr	nr	DE				
5335827	Male	17	6 days to blisters	nr	LT	OT			
FLUVOXAMINE									
1941501	Female	26	1 1/2 years	100	OT				
3714730	Female	72	? 15 days	50	HO				
PAROXETINE									
1343400	Female	47	nr	20	OT				
1379312	Female	63	60 hours	20	RI				
1564585	Female	43	? 1-2 months	20					
1632834	Female	69	nr	20	HO				
1917127	Female	40	38 days to onset - 8 days after dose increase	40	HO				
3013679	Female	53	>26 months	50	OT				
3057994	Unk	U	nr	nr	OT				
3125505	Unk	U	nr	nr	OT				
3139073	Female	24	a couple of months to onset, very noticeable after 6 months	60	OT				
3481691	Female	44	? 3 years	10	HO				
3669244	Male	23	nr	20	HO				
3814972	Male	31	?7 days	20	HO				
3917814	Female	31	14 days to onset, 19 days to dx	nr	LT	HO	DS	OT	RI
4132304	Female	52	long time	nr	HO				
4198002	Female	U	? 1 month	12.5	HO				
SERTRALINE									
960564	Unk	U	nr	nr	HO				
1412398	Female	54	? 6 days	nr	HO				
1436700	Male	72	4 days	50	DE				
1453836	Male	48	25 days	100	OT				
1627762	Female	22	? 3 weeks	20	HO				
1715220	Female	74	7 days	50	HO				
1759200	Male	U	nr	nr	OT				
1795224	Male	88	?5 months	nr	HO				
1919202	Male	80	? 2 weeks	50	OT				
1956155	Female	14	? 6 months	50	HO	RI			
3001088	Female	U	nr	nr	DE				
3129677	Male	14	nr	nr	OT				
3212092	Female	41	nr	100	HO				

3212721	Male	U	nr	nr	HO				
3414320	Male	65	nr	100	LT	HO	RI		
3677709	Female	36	45 days from start, 31 from dose increase	100	HO	RI			
3873596	Male	U	7 days to dx, 2 days to rash	50	LT				
3879174	Female	17	? 4 months	100	HO	RI			
3937855	Female	U	? 3 months from start, several days-1week after dose increase	50	HO	RI			
4415694	Unk	U	nr	nr	OT				
4712758	Female	37	11 days	?25	HO	OT			
4713146	Male	15	? 5 months	100	OT				
5129482	Female	30	3 days	25	HO	OT			
VENLAFAXINE									
1528570	Male	23	15 days to rash, 17 days to SJS dx	137.5	LT	HO	OT	RI	
1529913	Female	20	nr	nr	HO	OT			
1885597	Male	U	3 months		LT	HO			
1935919	Female	83	nr	nr	HO	RI			
3214525	Female	42	22 days	75	HO				
3217228	Unk	U	nr	nr	OT				
4167753	Female	71	? 1 month	nr	HO				
4273902	Female	62	6 days - only 1 dose on 10/4	nr	OT				
4299886	Female	76	nr	nr	HO	OT			
4410593	Female	21	nr	50	HO	RI			
4590277	Female	U	? 5 weeks after dose increase, 12 weeks after start	225	DE	HO			
4677929	Male	54	nr	nr	DE				
5384923	Female	49	nr	300	OT				
5424735	Female	U	nr	225	LT	HO			

7.6 DRUG USE DATABASE DESCRIPTIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

Verispan, LLC: Vector One®: National (VONA)

Verispan's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2.0 billion prescription claims per year, representing over 160 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients.

Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. Verispan receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

Verispan, LLC: Vector One®: Total Patient Tracker (TPT)

Verispan's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems. Vector One® receives over 2 billion prescription claims per year, which represents over 160 million patients tracked across time.

7.7 LIMITATIONS OF DRUG USE DATABASES

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that these selected SSRI's and SNRI's are distributed primarily in outpatient settings based on the IMS Health, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

Verispan's Vector One®: National (VONA) provides estimates of the number of prescriptions dispensed through outpatient retail pharmacies in the United States. Mail order is the second most common retail distribution channel for these products, accounting for up to a quarter of wholesale distribution during the year 2007. Mail order data estimates were not included in any of the outpatient retail data analyses, and therefore, may underestimate actual patient exposure.

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this page is the manifestation of the electronic signature.**

/s/

Lois LaGrenade
8/6/2008 04:31:00 PM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
8/6/2008 05:56:44 PM
DRUG SAFETY OFFICE REVIEWER

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Meeting of the Anesthetic and Life Support Drugs Advisory Committee

August 19, 2010

Eli Lilly and Company have submitted Supplemental New Drug Application for Cymbalta seeking an indication of chronic pain. In support of this indication, the applicant has submitted the results of two of three efficacy trials in chronic low back pain (CLBP) and one of two trials in osteoarthritis (OA). Cymbalta is already labeled with indications for the management of pain associated with diabetic neuropathy and for the management of fibromyalgia.

This committee will discuss whether the data support broadening the indication to chronic pain or if there are other options for broadening the indication, other than the current individual indications or chronic pain. This committee will also discuss the risk of hepatotoxicity based on the analysis of postmarketing data.

Discussion Points for the Committee

1. Discuss the data from the clinical trials in CLBP and OA and whether the applicant has provided adequate evidence of the efficacy of Cymbalta for these indications. Discuss whether there is evidence of increased efficacy of the 120 mg dose compared to the 60 mg dose.
2. Discuss the hepatotoxicity data and whether there is evidence that Cymbalta results in clinically concerning hepatic toxicity. Discuss the implications of the hepatotoxicity data in light of the applicant's request to expand Cymbalta's indication to the larger population of patients who suffer from chronic pain.
3. Taking into account the already approved indications for Cymbalta for the treatment of fibromyalgia and DPN, and the overall safety profile of this drug product, discuss whether the risk-benefit balance is appropriate for broadening of its indication to the treatment of chronic pain.